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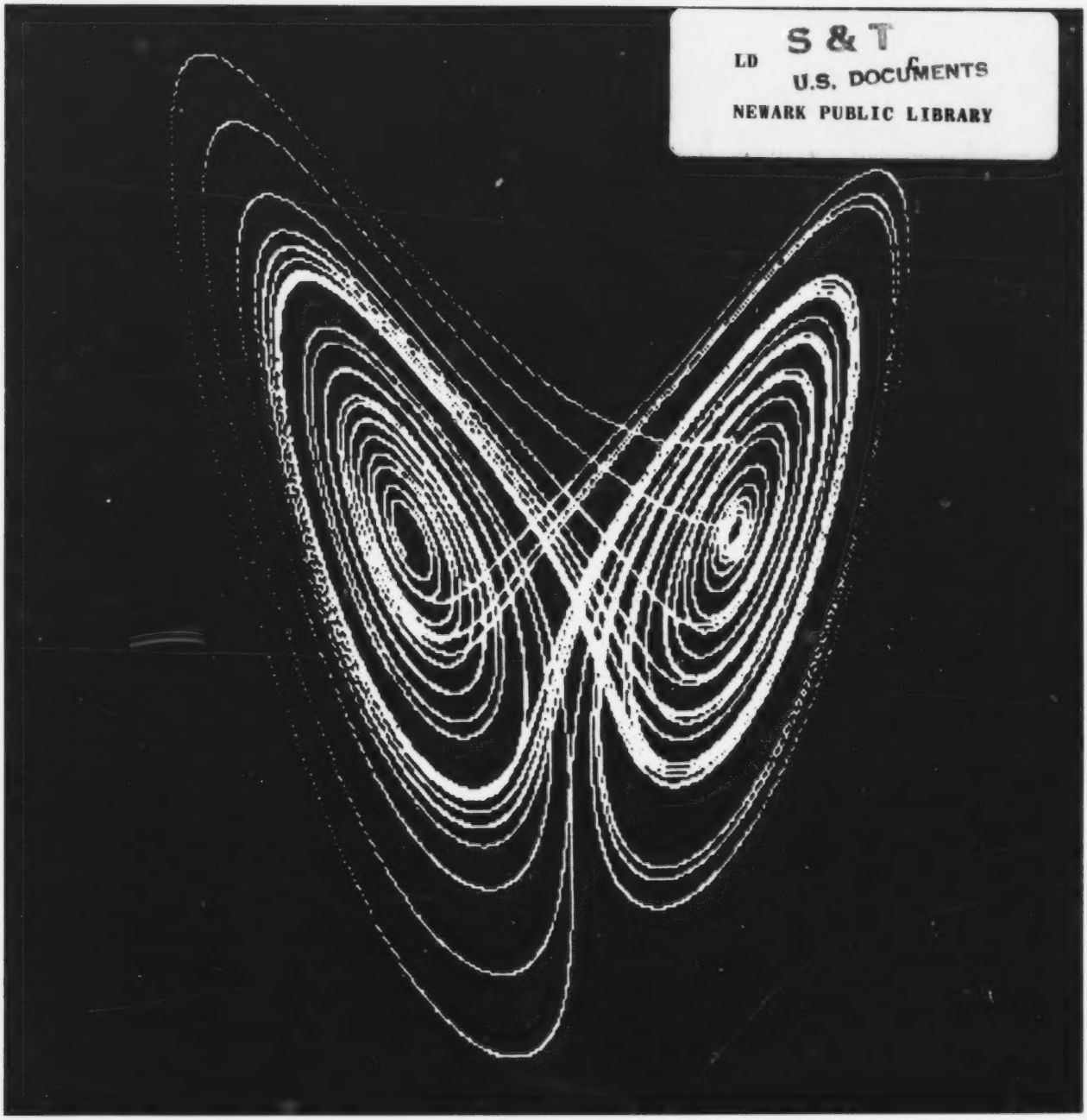

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In this *Mosaic*

This *Mosaic* carries an article by Edward Edelson on the increasing need in various scientific disciplines for solutions to problems that are showing themselves to be of a nonlinear nature. The assignment came about following an accumulation of references in *Mosaic* to the presence of nonlinearity in an expanding range of natural phenomena.

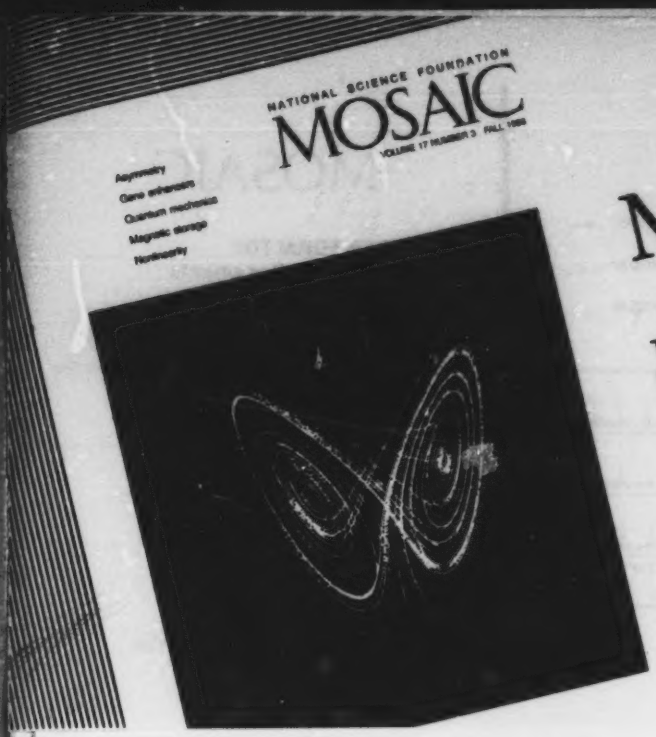
As Edelson reviewed what *Mosaic* had presented on the subject, he reported, "You seem to have picked all the cherries off this tree; this article is going to have to be about the tree." Like the legendary blind man and his elephant, we appear to have been describing what we could feel without knowing what we had under our hands all the time.

We might have known. For some time, writers handling an array of article assignments touching on nonlinearity had been tripping over each other's tracks, interviewing each other's sources, and exercising care to avoid duplicating the material in each other's stories. This is not entirely unusual; frequently, in the kind of interdisciplinary reporting *Mosaic* does, articles touch on subjects covered in earlier accounts, and we frequently refer to past articles in the effort to maintain continuity.

This time, however, we had another breed of cat, or elephant, or cherry, or metaphor: an array of stories that appeared to begin with Arthur Fisher's article on turbulence, "Disorder in Fluids" in Volume 15 Number 4, and hasn't ended yet. Since then there have been Edelson's "Another Kind of Conductivity," on sliding charge density waves, in Volume 15 Number 5; Mort La Brecque's "Fractal Symmetry," Margaret L. Silbar's "Physicists' Symmetries," and Fisher's "Chaos: The Ultimate Asymmetry" (for which he won the coveted American Institute of Physics Science Writing Award) in Volume 16 Number 1; T. A. Heppenheimer's "Routes to Chaos" in Volume 17 Number 2; and any number of the articles in the special *Mosaics* on research problems being addressed by the designers of advanced scientific computers, Volume 16 Numbers 3 and 4 and Volume 17 Number 1. Still to come are a pair of La Brecque articles on the number of subjects to which fractal mathematics is being applied, and another Silbar piece, on superstrings.

Certainly, we've addressed nonlinearity in other ways, and certainly, given its ubiquity, we'll address it again. There may be no merit in suddenly discovering that you've had an elephant under your hand for two years or more, but there is a certain comfort in knowing, finally, that you've been belaboring a pretty significant metaphor after all.

Warren Kornberg



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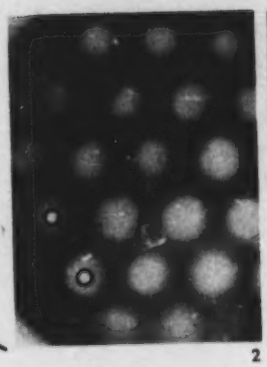

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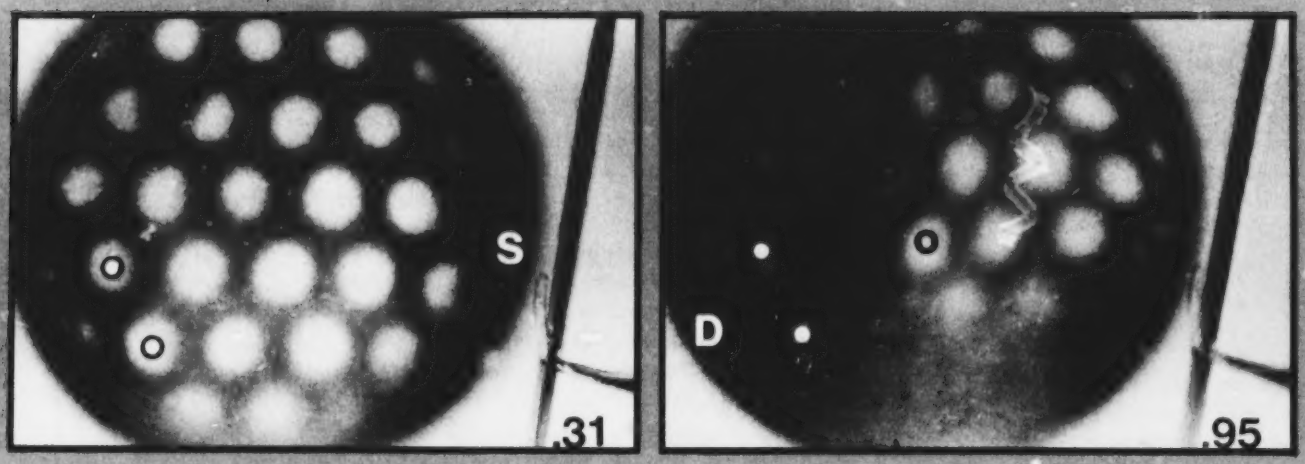
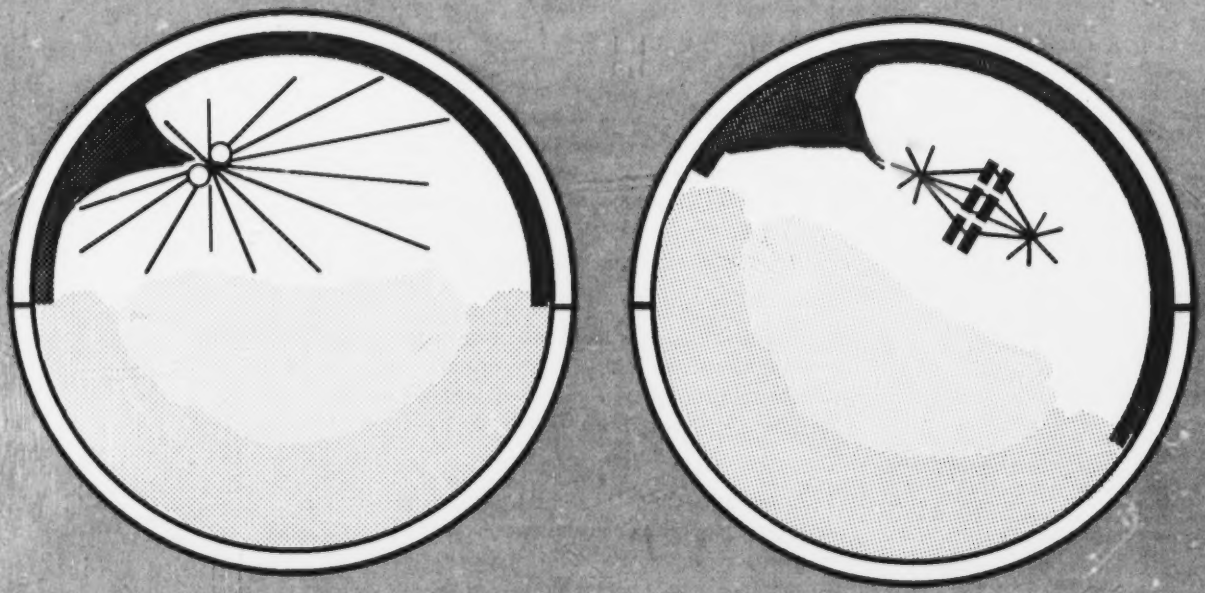
Determinants of Development

by David Holzman





The asymmetrical distribution of components within an ovum may have as much to do with the direction of embryo development as does the molecular nature of those developmental determinants.

In 1974 author David Rorvik created a stir with the book *In His Image*, which described the cloning of an old man from the DNA of his own skin cells. Paul Gross, director of the Marine Biological Laboratory at Woods Hole, says it is surprising that the book created even a ripple—especially among scientists—because such a cloning is in principle impossible. "If you wanted to clone me," says Gross, who has accepted an appointment as vice president and provost of the University of Virginia, "you would first have to get an egg from my mother." Even then, the resulting human being would not be identical to Gross because each egg is unique; differences in the egg become differences in gene expression from that which produced him.

Gross says the egg contains a secondary genome; its cytoplasm contains a storehouse of genetic information in the form of messenger RNA, some of which is localized (distributed asymmetrically) within the cells. This maternal legacy not only makes each egg unique, but it strongly influences early development, making it possible for a single cell of a fertilized egg to give rise to a multitude of tissue types, all of which contain the same genes. This phenomenon has been researched for more than 100 years and remains one of the oldest unsolved problems of biology.

The model that guides today's research was stated definitively in 1934 by Thomas Hunt Morgan, in his Nobel lecture. (Morgan received the Nobel prize for inventing drosophila genetics.) He presented the idea that so-called morphogenetic determinants distributed unevenly in the cytoplasm of the egg would guide growth and development by influencing the nuclear genes. The presence or absence of determinants, or perhaps their concentration gradients, would cause the nuclear genes of different cells to express themselves differently, creating different kinds of cells. The changed protoplasm of the different kinds of cells would then bring additional or other genes into action.

Xenopus. Microscopic view (top) shows movement of cytoplasm toward sperm entry. Drawing (bottom) shows aster and first mitotic spindle formed after sperm entry.

The concept of morphogenetic determinants in the egg goes back to 1878 when Charles Otis Whitman, who later became the first director of the Marine Biological Laboratory, published his doctoral thesis on the embryology of leeches of the genus *Clepsine*. Morgan's subsequent synthesis was additionally made possible by a long series of studies by many investigators supporting the idea of determinants; by the analyses of E. B. Wilson, E. G. Conklin, and others in the first decade of the twentieth century; by research that placed hereditary control in the nucleus; and by the rediscovery of Mendelian genetics, which came to dominate biological thinking between 1915 and 1925.

The difficulty of studying this fundamental concept can be measured by how often current research cites work of the previous century—almost as frequently as research in most other fields cites work of the previous decade. "Morgan became a first-rate geneticist of fruit flies largely because of the intellectual cul-de-sac he'd gotten into on the developmental mechanics of embryos," says Thoru Pederson, head of the Worcester (Massachusetts) Foundation for Experimental Biology.

It was not until the 1960s that the explosion of molecular biology made possible a deeper understanding of determination. The result has been a renaissance in studies of the problem approached from a number of angles. Several researchers are close to isolating determinants and deciphering their mechanisms.

A renaissance

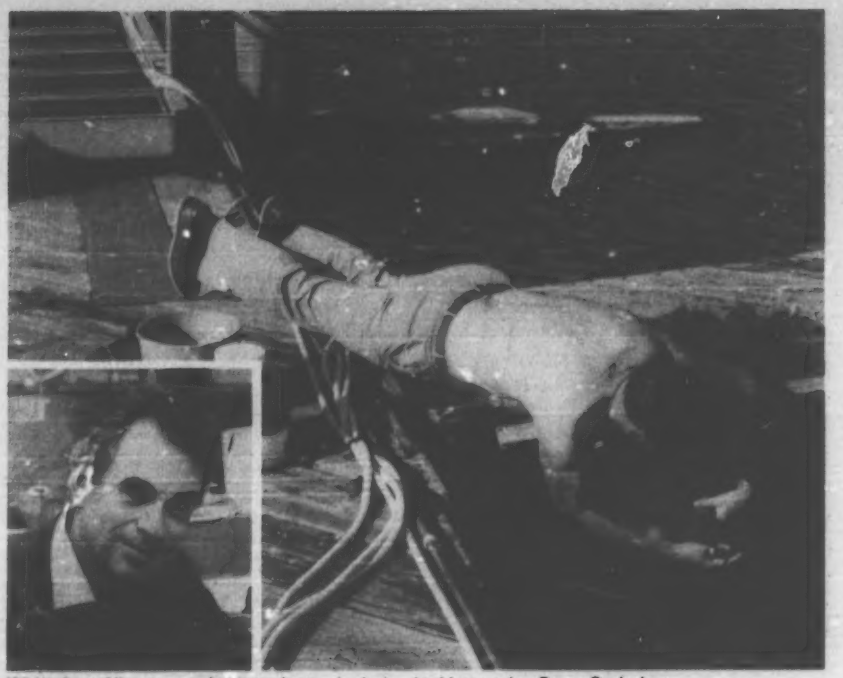
When Whitman began his work, scientists were studying embryology to cast light on the process of evolution. They believed, as Ernst Haeckel had stated, that "ontogeny recapitulates phylogeny"; that the developing embryo goes through stages that mimic the forms of its evolutionary predecessors. Whitman was among the first to apply reductionist principles. In his research on the leech, he traced the cell-by-cell origins of tissue types. He found that particular parts of the egg cytoplasm became particular parts of the embryo.

Under Whitman, the Marine Biological Laboratory became a hotbed of cell-lineage research, whose capstone was Conklin's 1905 study of cell lineage in the tunicate. The tunicate offers the unique advantage of naturally color-coded regions of its egg cytoplasm. In early development, these regions flow like the tectonic plates of earth in fast motion. Conklin's study of the egg to the 218-cell stage was the most extensive cell lineage study to that time. "I suppose it was [influential] just because it was so nicely done," says J. Richard Whittaker, currently an investigator of tunicate eggs at the Marine Biological Laboratory. But the color-coding of some cell lineages is more than just graphically appealing. It "shows predetermined localizations," he says.

The principle of early determination was supported by a variety of discoveries in the late 1800s and early 1900s, including that of micromeres. Micromeres are small cells that appear in the sea urchin at the 16-cell stage and that form the material for the larval skeleton. These cells can be removed from the embryo at the 16-cell stage. Without them, the embryo forms no skeleton; by themselves, in isolation, the micromeres do. In nematode worms, the chromosomes of future germ cells remain intact, while those of somatic—nongerm, or body—cells break up at the 4-cell stage. By artificially changing the position of the cleavage furrow so that a nongerm cell received cytoplasm from the germ cell, the chromosomes of the nongerm cell could be kept intact.

But the level of understanding of determination remained the same from the time of Morgan's Nobel lecture until the mid-1960s. The discovery in 1953 of DNA's structure and during the late 1950s and early 1960s of the chemistry of gene expression and regulation provided the foundation for a deeper understanding of embryonic determination. Modern techniques in molecular biology provided the means.

The primary genetic material DNA is transcribed to messenger RNA. The messenger RNA is then read on the ribo-



Whittaker. All-out search for tunicates includes looking under Cape Cod piers.

somes, the machinery that builds proteins. Certain protein molecules can in turn regulate genes by binding to DNA regions called promoters, upstream from the genes. The knowledge of the gene chemistry and expression provided embryologists with a focal point for the study of determinants and a model of how they might work.

An experiment in the early 1960s, by John Gurdon of Cambridge University, provided a picture of the condition of nuclear genes during development that was compatible with the emerging chemistry of gene regulation. The predominant view had been that in the course of development, cell lineages diverged from one another—to skin or liver, for example—because each cell type received a different subset of an organism's complete genome. This concept, called the variable-gene hypothesis, did not square with Morgan's paradigm. It was dealt a major blow in 1949 and 1950, when Hewson Swift of Columbia University established that the quantity of DNA remained the same in all cells throughout development.

Gordon removed the nuclei from fertilized frog eggs and replaced them with nuclei from the gut cells of tadpoles. Development of the eggs proceeded normally. This proved that all nuclei, and hence their genes; are equivalent in developmental potential. It supported Morgan's model of determinants as regulators of genes, turning them on and off rather than eliminating them from the genomes of developing cells.

Maternal messenger RNA

At the time that Gurdon was conducting his nuclear transplants, no one yet had a clue about the chemical nature of determinants. Paul Gross was not even thinking about determinants when he began the research that provided such a clue.

Gross had been concerned about some contradictions in the embryological literature. A variety of experiments had suggested that the nuclear genes play no part in early development. The nucleus could be killed—with X rays, for example—and yet development would proceed normally for a time, often until gastrulation. (Gastrulation is a time of large-scale rearrangement of the embryo, when it develops an inner layer of cells.) Other experiments had shown protein synthesis to be continuous during embryogenesis. Where was the protein coming from, if not from the expression of nuclear genes?

The easy answer, says Gross, but in principle not the only one, is that proteins were being translated from RNA that had been deposited in the egg earlier—during oogenesis. He gave this hypothetical egg RNA the name maternal messenger RNA. Most embryologists did not consider this to be a possibility because experiments in bacteria had shown that messenger RNA exists for no more than minutes before it decays, whereas early development continues for hours or days. But Gross thought that messenger RNA must last much longer in higher organisms than in bacteria, and he set out to test the idea.

Gross first tested his hypothesis by bathing developing sea urchin embryos in actinomycin, an antibiotic that prevents production of RNA without affecting DNA synthesis. "With messenger-RNA synthesis entirely shut down, protein synthesis continued for a very long time in those embryos. Early development continued to gastrulation and then stopped," says Gross. There was a lot of skepticism, Gross adds, "because the short-lived-message idea derived from microbial genetics was so convincing, and very few embryologists could do molecular biology anyway." Gross eventually proved the existence of maternal messenger RNA by molecular hybridization and by extracting it from the eggs and translating specific proteins from it in test tubes. Other researchers repeated the work in other organisms, and by the mid-1970s, maternal RNA's role as a critical genetic material of early embryogenesis was widely accepted.

Gross. Concerned about contradictions.

Holzman, who writes about biology, was author of "Ribosomal RNA: Where the Action Is," Mosaic Volume 16 Number 2.

According to Gross, the idea that maternal messenger RNAs might be morphogenetic determinants distributed asymmetrically followed immediately from the fact of their existence. It seemed obvious to Gross that the information content of an egg would be much greater if the RNA were distributed asymmetrically rather than uniformly. But techniques for plotting the distribution of RNA sequences in the egg were not then available.

Although Gross's early work did not prove that maternal RNAs or proteins translated therefrom were morphogenetic determinants, it provided so many tantalizing possibilities for control of development that it revived interest in the study of determination itself.

Bit by bit, researchers are closing in on the determinants, putting the first flesh of experimental data on the bones of Morgan's general model of determination. The primary approach has been to show that cytoplasm from one region of an embryo can transform cells from another region of the embryo into cell types of the first region. Then, in principle, researchers can isolate molecules of the determinant responsible for the transformation.

Shell coiling

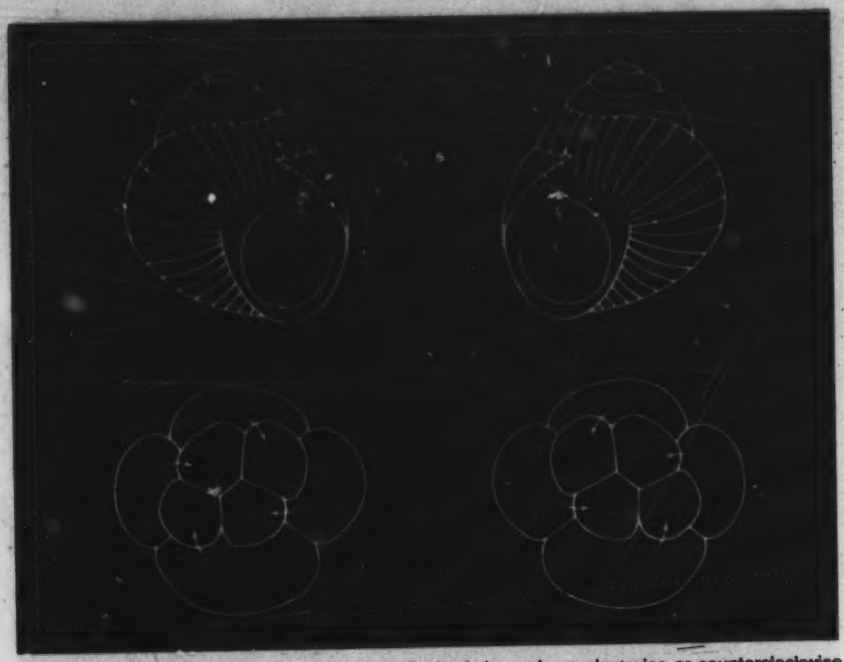
One of the simplest and most dramatic examples is transformation of the direction of shell-coiling in snails. Gary Freeman of the University of Texas has shown that left-coiling snails can be transformed into right-coiling snails by injecting cytoplasm from right-coiling snails into left-coiling embryos. The cytoplasm of left-handed embryos will not transform right-handed embryos.

This suggests to Freeman that the directionality is determined by a gene that produces a product in right-handed snails is lacking in left-handed snails. As further evidence that such a product exists, and is a determinant, Freeman finds that it appears during oogenesis and disappears early in embryogenesis, at the embryo's 8-16-cell stage. In these early stages, cell cleavage in the snail embryo occurs in a spiral pattern that corresponds to the direction of shell-coiling. "We have good information that [the gene product] is a protein," says Freeman. "The activity is destroyed by proteases [that degrade protein enzymes] and by heating [which denatures proteins]."

Freeman has been searching for the protein by separating extracts of right-handed egg cytoplasm on two-dimensional gels. (Two-dimensional gels sort proteins by size and by electrical charge.) He has been injecting protein samples into left-handed snails, in search of the molecule that will transform them. Once Freeman has found the protein, he plans to localize it with tagged monoclonal antibodies, to see where it goes and what it does in the developing embryo. He expects to find that it somehow changes the position of the mitotic apparatus.

Similar experiments have been performed in a wide variety of species. The Marine Biological Laboratory's Whittaker has distorted the position of cell cleavage in tunicate embryos so that nonmuscle precursor cells receive cytoplasm that would normally go to muscle precursor cells. The nonmuscle cell lineages subsequently produce acetylcholinesterase, an enzyme which occurs only in muscle cells of the tunicate. In *Drosophila*, Karl Illmensee and Anthony Mahowald induced germ cells, which normally form at the posterior tip, to form in the head and midventral regions of the embryo by injecting cytoplasm from the normal germ cell location to other parts of the embryo.

Whitman. Marine Biological Laboratory's first director; he introduced morphogenic determinants.



Snail spiral. Right vs. left coiling of adult snails (top) depends on clockwise or counterclockwise direction of spiral cleavage in the snail embryo's early development (shown by arrows, bottom).

Using staining techniques, they have shown that RNA is concentrated in the region of the germ cells and disappears after early embryogenesis. But they have been unable to isolate an RNA that by itself might be responsible for inducing the germ cells.

And in nematode worms, Reinhard Schierenberg of the Max Planck Institute in Göttingen, Germany, fused cytoplasm from a gut lineage precursor cell with a precursor cell from a different lineage. The fused hybrid produced gut lineage granules, structures specific to the nematode's gut lineage cells.

Kemphues. Identifying the determinants.

Ken Kemphues of Cornell University is taking an entirely different approach to searching for determinants. Kemphues studies genetic influence on the movement of P granules in the nematode worm egg. The P granules are tiny bodies, present in the egg at fertilization, that segregate to the germ cell lineage through development and that may contain determinants for this lineage. Prior to the first cleavage, P granules migrate to one end of the cell and remain in the same daughter cell after the first cleavage.

Migrant granules

Kemphues has found at least three genes that are necessary for localization of the P granules. Embryos mutant in any of these genes usually die. The dead embryos suffer from a variety of defects, says Kemphues. The P granules fail to localize. During the first few cell cleavages, the spindle, the apparatus that cleaves cells, is improperly oriented so that the daughter cells end up with some of the wrong cytoplasm. In the second cleavage, normally, the anterior cell divides before the posterior cell; in the mutants, both cells divide at the same time.

"It appears that all three loci affect all three processes," says Kemphues. He believes the systems that direct these processes are also responsible for localizing determinants, but he has no direct evidence of this. He says the only evidence that this localization controls any determinants is first that the few mutants that survive to adulthood contain neither germ cells nor P granules, and second that mutants at two of the loci he studies fail to produce gut cells.

Attempting to identify the determinants, Kemphues plans to clone the genes that control the localization systems, sequence the proteins coded for by those genes, and then study those proteins. He hopes these might give him some insight into what the determinants are, but he admits that his approach is a gamble. "Will we use those [proteins from the localization genes] to find out what is being localized? Right now I don't see a clear way to do that."

Furthermore, Kemphues speculates that "determinants are not discrete entities, but a collection of things that creates a physiological state in one cell. . . . The granules are one requisite, but not the whole story."

Suggestive studies

These studies are all suggestive of determination, but lack proof because none of these researchers has isolated a specific determinant molecule. That determinants could be RNAs or proteins encoded by them is nonetheless suggested by several studies which have found some RNAs to be asymmetrically distributed in egg cells or early embryos. In the late 1970s Gross found that certain RNAs were distributed asymmetrically in the sea urchin at the 16-cell stage. At that point in development, the embryo contains three types of cells. One set of cells, the micromeres, eventually becomes skeleton. Gross and his colleague William Rodgers compared the nonribosomal RNA sequences of micromeres with the RNAs of the other two types of cells present at that stage. The micromeres differed from the other two types of cells in about 15-20 percent of their RNA sequences.

More recently, William Jeffery of the University of Texas has shown that RNAs are localized in the eggs of tunicates and furthermore that the cytoskeleton appears to sort the RNAs. By using centrifuging, a technique that separates objects by size and density, he found

that the RNA molecules in the eggs moved with the much larger cytoskeletal structures rather than according to their intrinsic size. He plotted the positions of the RNAs using the new technique of in situ hybridization.

Jeffery believes that a combination of timing and movement is responsible for segregating the RNAs. For example, the region of the developing egg near the nucleus can be thought of as a train station where all trains leave from the same track for different destinations at different times. Different RNAs transcribed in the nucleus are timed to meet cytoskeletal elements that have the proper destination, according to Jeffery's model.

Although Jeffery is just beginning to investigate this model, Rudolph Raff of Indiana University has evidence that eggs can indeed segregate substances by timing. Most of the messenger RNA in unfertilized sea urchin eggs is located in the cytoplasm, but five RNAs, all of which code for histones, are associated with the nucleus, says Raff. "Those histone messages are released two hours after fertilization; the others are translated to protein right after fertilization."

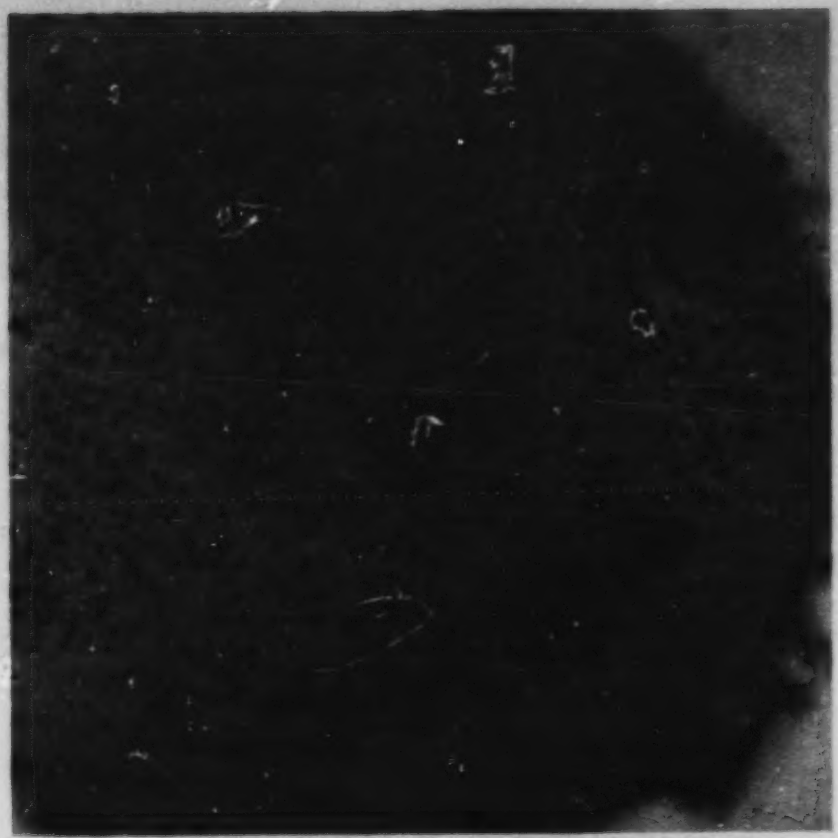
Working on eggs of the frog genus *Xenopus*, Douglas Melton of Harvard University has isolated molecules that may be determinants. Melton has found specific RNA sequences concentrated in several regions of the egg. The striking localization of these RNAs suggests that they may play a role in cell fates. This can now be tested, he notes, by using a new method to assay gene function in developing embryos.

Jeffery. Combining timing and movement.

Nematode embryo. At the four-cell stage, normal embryo shows granules only in one cell (top), while the mutant, at the same stage, has granules in all four of its cells (bottom).

Melton's experiment uses an ingenious method for investigating the function of the localized RNAs. The method takes advantage of the fact that RNA molecules are normally single-stranded, as they must be for translation to protein to occur. But strands of RNA with complementary sequences may form double helices like those of DNA. Melton has created strands that are complementary to the localized RNA, which he calls anti-sense RNA. He refers to his sense/anti-sense double helices as artificial mutations, because they prevent the translation of maternal messenger RNA.

Kathryn Anderson, now of the University of California, Berkeley, and Christiane Nüsslein-Volhard of the Max Planck Institute in Tübingen, Germany, have come nearly as close as Melton to isolating determinants. Working with fruit flies that were mutant in any one of seven genes, the two researchers found that they could induce near-normal development by injecting cytoplasm from normal embryos—a process they call rescuing the mutants. Then they found that they could induce near-



Tunicate egg. RNA probe shows uneven distribution of mRNA within the developing egg.

normal development by injecting cytoplasm from an embryo that had a mutation in a different gene. They then isolated maternal messenger RNA from the cytoplasm of normal embryos (without distinguishing among coding sequences) and also used that to induce near-normal development.

Anderson. Rescuing the fruit fly mutants.

Most of their colleagues think there must be determinants in the RNA Anderson and Nusslein have isolated, or in the proteins encoded therein. Nonetheless, a variety of factors complicates interpretation of this experiment, leading Anderson to conjecture, as Kemphues did, that determination may be a physiological state in the cell, brought about by more than one factor.

The seven mutants all look the same. They are what Anderson calls dorsalized, which means that structures normally associated with the dorsal side grow out of the ventral and lateral sides as well, and that normal ventral and lateral structures fail to grow. Also, the mutants vary in the degree of normal development that can be induced. Only one becomes totally normal. Weak rescues are characterized by the appearance inside the larval respiratory-tract openings of structures called *filzkörper*, or felty bodies. Heralding strong rescues are denticles, toothlike appendages of the ventral surface which larvae use to crawl through food. "The ultimate degree of rescue," says Anderson, "is when the embryo hatches."

Gerhart. Arresting the rotation of the egg.

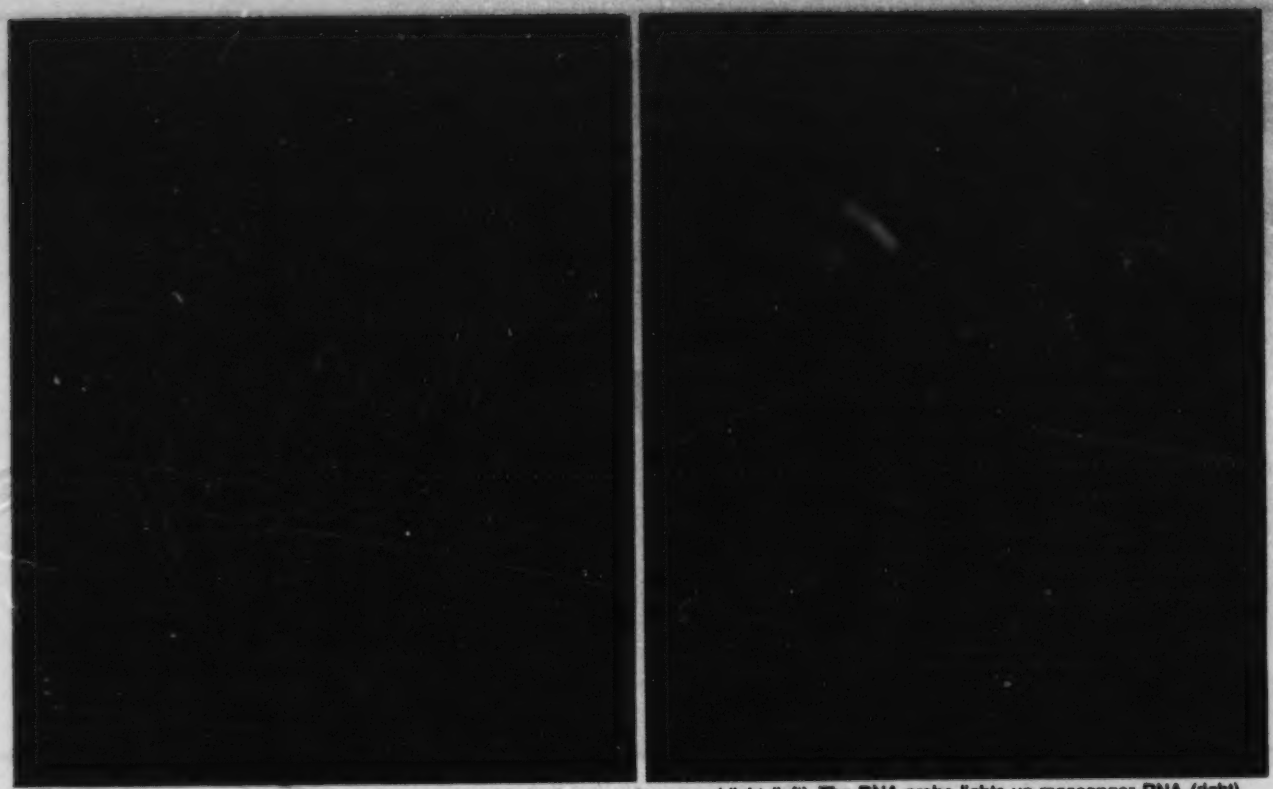
All this suggests to Anderson that all the genes are working together in some fashion, but "what working together means is not clear," she declares. Gene products "could be steps in a biochemical pathway, subunits of a multimeric protein, or some [of the gene products] could be involved in regulating others. But in some sense they are all essential for a single process."

For each mutant, the researchers can modulate the degree of rescue by modulating the amount of RNA or cytoplasm they inject into the egg. That a low concentration of RNA would make the more dorsally placed felty bodies appear, while a higher concentration would induce the ventrally placed denticles to appear as well, suggests to Anderson that determination is based on gradients of the substances, rather than their absolute presence or absence. This means that in the normal egg, one would expect a high concentration of determinant ventrally, and a low concentration dorsally, rather than the simple presence of a determinant ventrally and absence dorsally.

Activation

The problem is that for one mutant, which Anderson calls toll, the point of the injection of normal RNA becomes the ventral pole of the axis, changing the positions of all structures in the embryo. This could suggest that the distribution of the toll gene product defines ventral to the embryo.

But later experiments indicating that the toll gene product is uniformly distributed forced her to develop a more complicated explanation. Anderson has developed a model of determination as a physiological state to account for her observations. She thinks that the toll gene product is a self-activating, poorly



Sea urchin. At Raff's laboratory, a developing young urchin is shown under normal light (left). The RNA probe lights up messenger RNA (right).

diffusible determinant that interacts with a highly diffusible inhibitor substance. But she cautions that the model does not perfectly fit the data.

However, her observations share peculiar similarities with those her Berkeley colleague John Gerhart has made on an entirely different creature, the frog *Xenopus*. Prior to the first cell cleavage, the entire surface of the egg of *Xenopus* rotates 30 degrees with respect to the interior, like the crust of earth flowing over the molten core. Using a variety of strategies, Gerhart and his student Stan Scharf have arrested the rotational process at different degrees of rotation. If rotation is prevented from occurring, the embryo is stunted in a manner similar to that of Anderson's dorsalized mutants. The greater the degree of rotation, the more development of bodily elements, beginning with tail, then continuing with trunk, hind-brain, and so forth. A double rotation actually creates twins.

Raff. Time delay in sea urchin eggs.

"The old idea is that you would have determinants for the notochord scattered around the egg," says Gerhart. "Then all the determinants would become concentrated in one place, and that is where the notochord would grow." Gerhart says the result of twins from a double rotation creates problems for that interpretation. In a drosophila model that parallels Anderson's studies, Gerhart thinks inactive determinants that are activated by the rotation may exist everywhere in the embryo.

Isolating determinants is only the first step toward filling in Morgan's model. The next step will be to show how they act upon the nuclear genes to cause differential expression in different parts of the embryo. Eric Davidson of Caltech and Robert Angerer of the University of Rochester have already shown that different genes are activated in different places during early embryogenesis, but no one has shown which determinants are responsible for this. "If I were able to go ahead with the obvious next steps in the maternal-messenger-RNA story," says Gross, "I would attempt to localize specific maternal messages, and their products, that alter the behavior of chromatin. (Chromatin is the material that contains the DNA; it can influence how genes are expressed.)

Meanwhile, J. Richard Whittaker is "not entirely sure that [determinants] exist as loose chemical entities. . . . I design my experiments as though it were true," Whittaker says, " but I keep it in the back of my mind. We may come across some anomalous results in these experiments that may point to an entirely different theory." ●

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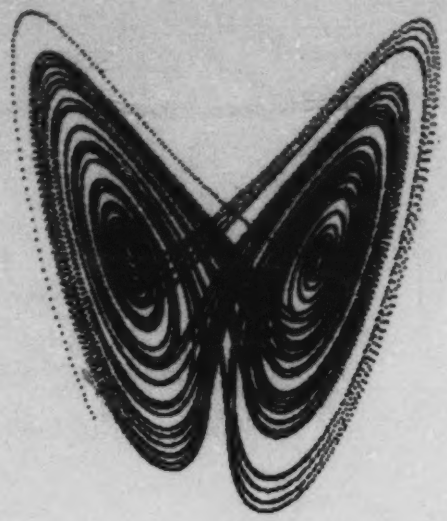
THE UBIQUITY OF NONLINEARITY

by Edward Edelson



Order in chaos. In series of computer graphics with varying factors, butterfly-shaped strange attractors appear from Lorenz's simulations of weather predictions.

Computing power and a range of new concepts are making it possible to study natural phenomena on their own beguiling nonlinear terms.

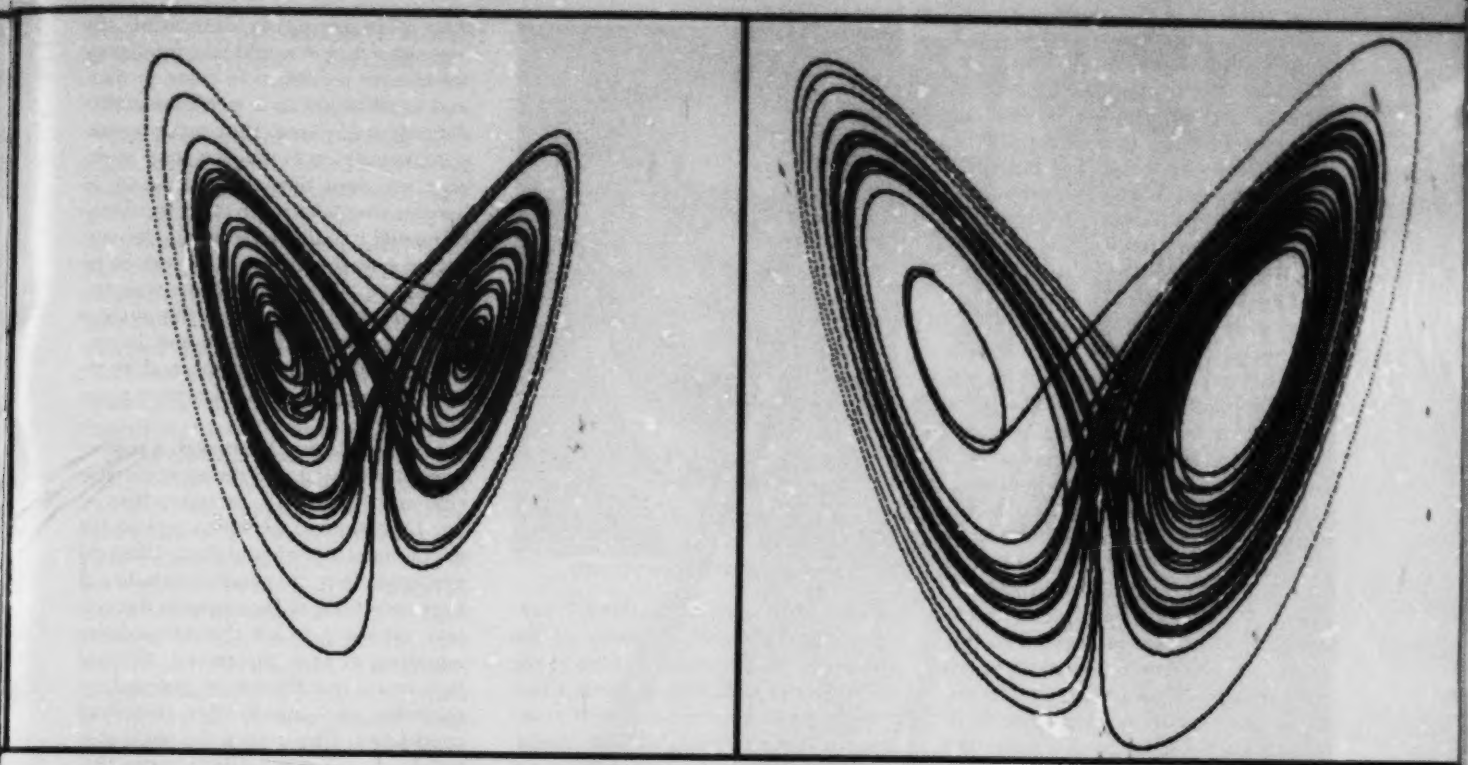
A wind tunnel is an insult, John von Neumann once remarked. Von Neumann, one of the greatest of all mathematicians and a father of the digital computer, explained that engineers were forced to build what amounted to a giant analogue computer to obtain the data they needed, because they were unable to calculate the aerodynamic properties of aircraft.

In a lecture delivered in 1946, von Neumann made his criticism more general. His subject was the potential effect on mathematics of "large-scale, automatic computing instruments," which were just coming into existence. They were needed, von Neumann said, because "our present analytical methods seem unsuitable for the solution of the important problems arising in connection with nonlinear partial differential equations and, in fact, with virtually all types of nonlinear problems in pure mathematics." Efficient computing devices, he said, could make the difference "in the field of nonlinear partial differential equations as well as many other fields which now are difficult or entirely denied of access."

Von Neumann, as usual, was right. The arrival of the digital computer has had exactly the effect he predicted on the study of nonlinear systems. "Today, thanks in large part to computers, many previously intractable nonlinear problems have been solved, and the field of nonlinear studies has come into its own," a recent review paper said.

This new field, nonlinear science, is made possible by many converging factors; the availability of computers is only part of the story. Equally important is the development of several concepts, or paradigms, that for the first time give scientists models that allow them to deal with the extraordinarily complex behavior of real-world systems. Advances in mathematical techniques are another important contribution that can be applied to nonlinear systems.

Von Neumann emphasized nonlinear partial differential equations because, essentially, the world is nonlinear. Only a few phenomena can be described by a linear model, one in which a given input produces a proportionate output. A flag that waves in a gentle breeze is a linear system because its ripples are smooth and have a size proportionate to



the wind velocity. But if the wind becomes strong and gusty, the flag will begin to snap violently and release its energy in unpredictable spurts. The higher input of energy turns the flag into a nonlinear system.

Similar nonlinear systems, from the smallest scale to the largest, are everywhere in nature. Water flowing through a garden hose, local and global weather patterns, and the development of a complex living organism from a single fertilized cell are all nonlinear phenomena. Even the pendulum, an apparently simple system, does not exhibit entirely linear behavior under all conditions: If the pendulum is driven by the addition of energy, if its motion is damped, or if the angle through which it swings is large, then it can move from linear behavior, in which the governing equations are linear and in which the period of its motion is a constant, into nonlinear, unpredictable motion.

The pendulum example is instructive because many historians date the beginning of the modern scientific era to Galileo's development of the simple linear equations that described the motion of a pendulum. He observed the pendulum—actually a chandelier swinging in the cathedral at Pisa—over the limited range of activity in which its behavior was linear; with hindsight, it can be seen that in the process he pioneered a method—and a limitation—that has been at the center of scientific achievement ever since.

Nonlinear science

In the three centuries since Galileo, countless scientists have spent their time extracting from complex systems those elements of behavior amendable to treatment by linear equations. The power of this method lies in the fact that solutions to linear equations can be added together to produce other solutions. By breaking a linear system into many parts, each describable by a linear equation, it is possible to come up with a solution that describes the entire system. In contrast, the equations that describe a nonlinear system—the snapping flag, the damped or driven pendulum—cannot be manipulated in that way because if two solutions to a nonlinear equation are added together, another solution does not result. The scientist or mathematician who deals with a nonlinear system must work with it in its full complexity. Von Neumann, realizing the complexity of the resulting mathematics, knew that a first step toward scientific understanding of nonlinear systems had to be the provision of powerful computing machinery.

In addition to its reliance on computers, the field of nonlinear science has several striking features. One is its strongly interdisciplinary nature. The paradigms that describe nonlinear phenomena are applicable in disciplines that traditionally have had little in common. "The psychiatrists at UCSD never used to talk to the oceanographers," says Henry Abarbanel of the University of California at San Diego, "but now they do." The reason is that subsurface currents in the ocean and the propagation of impulses along nerve cells can both be described by the same concept, the soliton, Abarbanel explains.

Another feature of nonlinear sciences is its strong dependence on computer graphics. Visual displays are essential because of the huge amount of data generated in nonlinear studies. These data simply are not comprehensible in tabular form; graphics are needed to extract a meaningful signal from them. "You cannot read a billion numbers," says Karl-Heinz Winkler of the Los Alamos National Laboratory. "But I can encode a billion numbers for you in a four-minute film."

The rise of nonlinear studies has a number of potentially revolutionary implications. One phenomenon that exhilarates some observers and disturbs others is a potential basic change in the nature of mathematics. For millenia, mathematics has been an a priori discipline in which the basic requirement has been rigorous proof of any proposition. But mathematicians and scientists working in nonlinear studies now commonly deal in what they describe as experimental mathematics, in which a proposed solution to a problem is run on a computer and is modified according to the results of the run. Because there can be no rigorous proof in this kind of experimental mathematics, many older mathematicians are alarmed by the possibility that the foundation of their discipline, which has existed at least since Euclid, will be dissolved, causing permanent and irreparable damage. Nonlinearists respond to this perceived threat by noting that experimental mathematics can provide the basis for rigorous development; it allows mathematicians to determine the relationships among different parts of a complex problem.

A challenge of a different sort, to both scientists and the agencies that fund them, comes from the interdisciplinary nature of nonlinear studies. Grave psychological and organizational problems arise, for instance, when the same model can be used to study the dynamics of a protein, the Red Spot of Jupiter, and the transmission of signals through optical fibers. Joseph Ford of the Georgia Institute of Technology, a pioneer in nonlinear studies, says that he has had little success in establishing collaborative programs with colleagues in his own institution, but he is working fruitfully with groups in Milan, Italy and Novosibirsk, the Soviet science city.

Efforts to break down these barriers have begun. For example, Los Alamos National Laboratory has established a Center for Nonlinear Studies, and a program to link six campuses of the University of California in an Institute for Nonlinear Sciences is under way. Similar efforts are also said to be under way at Cornell, Arizona, Princeton, Harvard, and locations in Europe.

One driving force for the new discipline of nonlinear science is the existence of a number of models, or paradigms, for natural systems that were previously too complex to handle.

Abarbanel. Psychiatry, oceanography.

"It is a new way of thinking," says Heinz-Otto Peitgen, formerly of the University of Bremen and now at the University of California at Santa Cruz. "We begin to understand with some surprise that problems that were considered inaccessibly hard share crucial qualitative properties with incredibly simple model systems; this is the phenomenon of structural stability that physicists call universality," he says.

Developed largely in the past two decades, the paradigms of nonlinear science are still in their infancy. These paradigms do not describe a nonlinear system exactly, says David Campbell, of the CNLS at Los Alamos, but they do provide conceptual frameworks for the understanding of nonlinear phenomena. Campbell lists three major paradigms: solitons, chaos, and fractals.

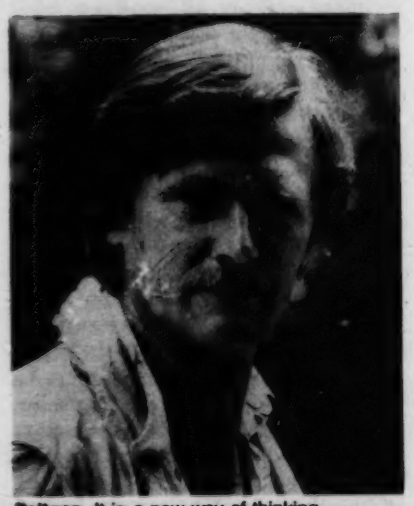
Solitons

The soliton story begins in 1844, when a British naval designer, John Scott Russell, was watching a boat being drawn along a narrow canal by horses. When the boat stopped suddenly, Russell wrote, the wave in front of it "rolled forward with great velocity, assuming the form of a large solitary elevation. . . . I followed it on horseback and overtook it still rolling on at a rate of some eight or nine miles an hour, still preserving its original figure. . . ."

The solitary wave that Russell described evolved into the soliton through the work of several people. One seminal experiment was done in 1955 by Enrico Fermi, John Pasta, and Stanislaw Ulam, who were trying to determine the amount of time it would take for a long-wavelength oscillation to come to thermal equilibrium in a nonlinear, one-dimensional system. They set up a computer simulation in which a wave of energy was sent through a chain of 64 weights coupled to each other by identical, weakly nonlinear springs. They expected that the energy soon would be divided equally among all the weights. Instead, they found that the system tended to come back to its original form, with the initial wave motion and its related harmonic motions occurring again and again.

In 1960, Martin D. Kruskal, a mathematical physicist at Princeton University, and Norman J. Zabusky, then at Bell Laboratories, set out to explore the implications of the Fermi-Pasta-Ulam experiment. They did computer studies of the interactions of the waves in the system, expecting to see the waves disintegrating as they interacted. Instead they found that the waves emerged essentially unchanged after they had overlapped. They coined the word soliton to describe a solitary wave that emerges unchanged from such an interaction. Out of this initial impetus grew a description of soliton dynamics involving an interplay among several diverse areas of mathematics and physics.

Pure solitons are rarely found in nature, but many phenomena in widely different fields can be described in terms of solitonlike behavior. "From vortex eddies in turbulent fluids through clumps of electromagnetic fields in plasmas to self-trapped electrons in conducting polymers, spatially



Peitgen. It is a new way of thinking.

localized, long-lived excitations abound in nonlinear systems," says Campbell.

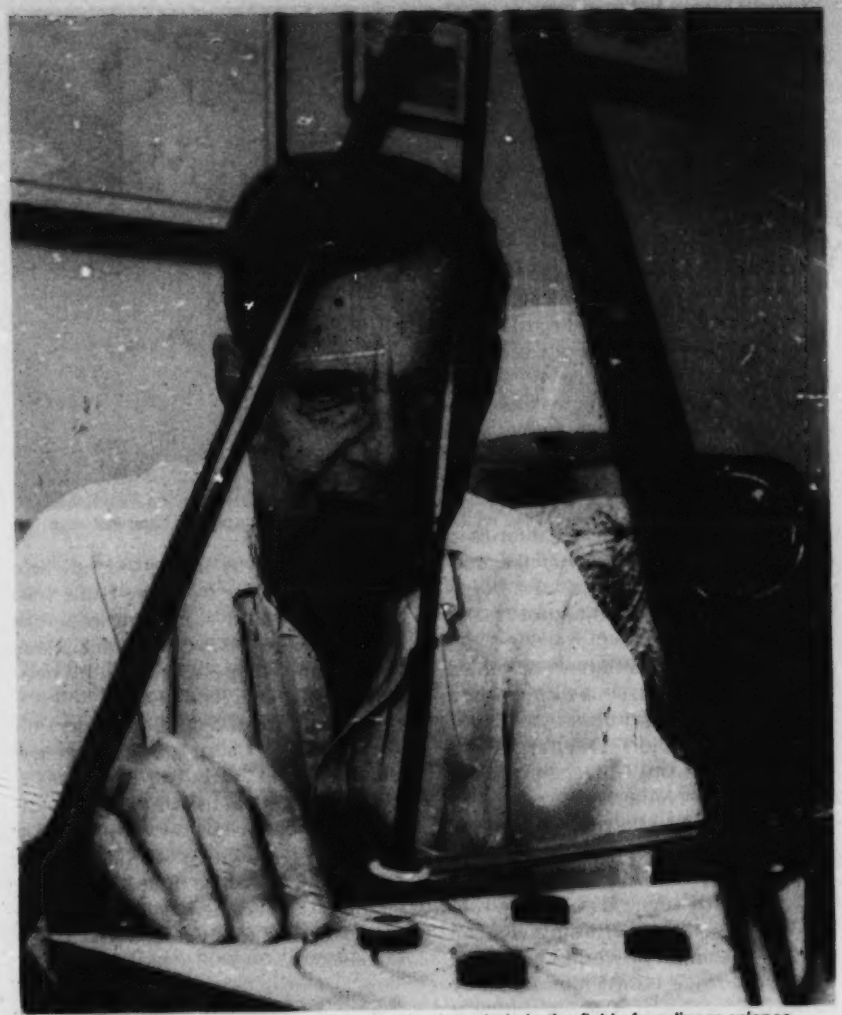
Chaos

The development of a second paradigm, chaos, can be traced back to the insights of the great French mathematician, Jules-Henri Poincaré, who has been described as the last individual capable of comprehending all of the mathematics of his time. In the course of an incredibly fruitful lifetime of work that spanned the late nineteenth and early twentieth centuries, Poincaré came to realize that some problems were outside the reach of existing methods.

These methods had been derived to describe the "clockwork" universe of Pierre-Simon Laplace and René Descartes where, at least in theory, complete knowledge of the current state of every element of the system allowed its entire future evolution to be described. Poincaré realized that, in practice, the state of each element had to be known to infinite accuracy to predict the future of the system. But any physical measurement of a system will contain some small error, so two systems whose differences were so small as to be imperceptible would evolve along completely different pathways. In such systems, Poincaré wrote in 1908, "small differences in the initial conditions produce very great ones in the final phenomena. A small one in the former will produce an enormous error in the latter. Prediction becomes impossible, and we have the fortuitous phenomenon." In current terminology, Poincaré was saying that chaos—apparently random behavior—could be found to occur in deterministic systems.

That was a chilling insight for those who hoped to extend the scientific understanding of nature. Even more chilling was the knowledge that some chaotic behavior could be exhibited by extremely simple systems. Perhaps the classic example is the three-body problem, the calculation of the orbits of any three bodies such as planets around each other. A two-body problem is easily solved by Newtonian physics. The three-body problem, Poincaré found, is unsolvable—not because the mathematics is too difficult, as was originally thought, but because three-body orbits can behave chaotically.

A major achievement of the past few decades is the demonstration that order can sometimes exist within chaos—enough order to give nonlinear scientists a hold on systems that exhibit chaotic behavior. The work done on the unpredictability of weather systems by Edward Lorenz at the Massachusetts Institute of Technology in the early 1960s led to one concept of major importance in the study of chaos.



Ford. At Georgia Tech, one of the more imaginative minds in the field of nonlinear science.

Lorenz showed that the weather is inherently unpredictable, because the atmosphere is a system that exactly meets the description given by Poincaré: It is exquisitely sensitive to small changes in initial conditions. In one paper, Lorenz noted that the beat of a butterfly's wing can cause unpredictable changes in the weather patterns of an entire terrestrial hemisphere.

Order began to emerge from chaos when Lorenz used computer graphics to do simulations of a much simplified model for global weather patterns. An unusual, butterfly-shaped figure appeared as the simulations ran on. The existence of the figure showed that although the atmosphere is (in the scientific sense) chaotic enough to make weather unpredictable for more than about ten days, there is enough order within the chaos to make some reasonably accurate predictions possible over the short term. (Interestingly, on a scale of months or years, the weather is predictable on the average. Season by season, weather patterns can be predicted more accurately than next week's weather. The seasons thus can be described as weakly stable attractors in overall weather patterns.)

Today, the figure that Lorenz saw on the computer screen is called an attractor—a strange attractor, to be precise. An attractor can be described as a set of states to which the system tends to go.

(It goes to the whole set, not to a single state, except in especially simple circumstances.) For a pendulum that is set swinging, the attractor is the point at which the pendulum settles as its energy dissipates. If the pendulum is driven continually, the attractor becomes more complicated. The figure seen by Lorenz has an extraordinarily complex structure. It can give only a partial prediction about the future state of the chaotic system. The system will tend toward the set of states described by the strange attractor, but imperceptible differences in initial conditions will lead the system toward totally different paths along the strange attractor. Lorenz's finding went largely unnoticed outside of meteorology, but others were pursuing similar lines of thought. In 1963, Stephen Smale of the University of California at Berkeley described a closely related object, called the horseshoe, and began the systematic underpinning of chaotic dynamics.

The term strange attractor was coined in 1971 by David Ruelle, a mathematical physicist at the Institute of Advanced Scientific Studies in France, and Floris Takens of the State University of Groningen in the Netherlands, who proposed that fluid turbulence—one of the most intractable problems in science—could be described in terms of strange attractors. That suggestion, highly controversial at the time, stimulated an enormous amount of work. One of the most productive efforts was made by Mitchell Feigenbaum, a physicist then at Los Alamos National Labratory and now at Cornell University. He was interested in the transition to chaos, such as occurs when flow in a fluid changes from steady to turbulent as its velocity increases. He identified period doubling (the successive doubling of periods of recurrent motion) as a key ingredient in the transition to chaos.

Feigenbaum found that the rate at which period doubling occurs in a number of totally unrelated systems could be described by the same constant. The ramifications of such discoveries about chaotic systems are only beginning to be explored. The central fact is that work on chaos, as is the case with solitons, provides a model for understanding nonlinear phenomena.

A third paradigm, fractals, originated in the work of Benoit Mandelbrot, a mathematician who was born in Poland, educated in France, and is now em-

Campbell. Solitons, chaos, and fractals.

ployed by IBM. A fractal—Mandelbrot derived the term from the Latin verb *frangere* (to break)—can be described as a mathematical shape that is analogous to the many shapes generated by nonlinear systems in nature.

A more formal definition centers on the fact that a fractal has a noninteger dimension. In Euclidean geometry, a point has no dimension, a line one dimension (length but no width), and a plane has two dimensions (length and breadth). A fractal fits none of these categories. It can be a shape that appears to fill most of a plane but still not have two dimensions.

A gallery of monsters

The value of the fractal, says Michael Barnsley of Georgia Tech, is that "it frees science from the tyranny of the straight line." Mathematicians began breaking free of that millenia-old tyranny in the nineteenth century. One significant early event came in 1872, when Karl Weierstrass constructed a curve so irregular that no tangent could be drawn to it at any point. Others—Georg Cantor, Guiseppe Peano, Felix Hausdorff—later drew many such irregular lines that had noninteger dimensionality and violated other rules of Euclidean geometry.

The idea was unsettling. Even Poincaré called the curves "a gallery of monsters." One of Mandelbrot's major achievements was to show that such curves could be used to describe the complexity found in nature. Mandelbrot began with fractals that are self-similar; that is, they look the same at any level of magnification. In a series of papers, he showed that nature abounded with such self-similar shapes. One such shape, Mandelbrot said in a pivotal paper in 1967, is the coast of England (or indeed, of any island).

How long is the coastline of England? Mandelbrot asked. His answer: No one can say! The length established by an observer using a picture taken from a spacecraft is different from the length measured by someone who goes along the coast, measuring fine detail inch by inch. (Which explains why equally reputable reference works carry strikingly different estimates of the lengths of various national borders.) But there is a constant in these measurements, Mandelbrot notes—the fractal dimension, defined as the relationship between the scale of measurement and the length of coastline determined by that measurement. The fractal dimension of the British coastline is 1.26.

Mandelbrot and others soon used the power of the computer and the concept of fractals to produce remarkable images—artificial but realistic—of mountains, continents, and planets. Other families of fractals that are not self-similar have been developed. The full implications of these so-called nonlinear fractals (one of the most interesting is called the Mandelbrot set; another is the Julia set, named after one of Mandelbrot's teachers, Gaston Julia) are just beginning to be explored.

The images produced by the combination of computer graphics and fractals are so intriguing that they have become an art form. For example, fractal images made at the University of Bremen were put into an art show exhibited in Europe and the United States.

One set of them was developed on the basis of a suggestion by physicists C. N. Yang and T. D. Lee in 1952 about the possibility, realized only recently, of displaying the phase transition from magnetic to nonmagnetic behavior. "We now believe we know why it took so long," Peitgen and a colleague, Peter H. Richter, wrote in the catalogue of the exhibit. "The complex phase boundaries are in fact Julia sets! . . . In many respects this is not a realistic display of magnetism, but it allows one to see connections which are completely obscure in better models."

Fractals are being used to describe the flow of water in soil, the distribution of vortices in turbulent flow, the structures of polymers—the list goes on. Like the

other paradigms of nonlinear science, fractal uses are as endless as the real world is complex.

The paradigms often interlock. For example, Peitgen and Richter point out that "the Mandelbrot set embodies a principle of the transition from order to chaos more general than the Feigenbaum universality. The esthetic charm correlates with a more fundamental meaning, as is often the case in mathematics." As David Campbell puts it, "Basically, Mandelbrot has shown that fractals provide the natural geometry for describing chaos."

At Los Alamos, a group including Harvey A. Rose, Gary G. Doolen, and Don DuBois is studying the interaction of beams of radiation—laser light or charged particles—with plasma, a study of great practical importance in fusion energy research. The aim is to get enough energy from a laser or charged particle beam into the plasma to cause hydrogen nuclei to fuse. This achievement has been thwarted because of instabilities that cause energy to go to electrons. This undesirable energy transfer occurs because the plasma develops regions of high-frequency electric fields and low density. These so-called cavitons, first described in 1972 by a Soviet fusion physicist, V. E. Zakharov, have characteristics of and exhibit chaotic behavior, DuBois says.

Experimental work by A. Y. Wong and others at the University of California at Los Angeles shows that a caviton arises when a localized area of high electric-field density, called a Langmuir wave, is excited by a high-energy beam. The result is "a turbulent collection of solitons" that quickly collapses, transferring its energy to electrons. The burnt-out caviton can become reexcited, starting the cycle again.

Mandelbrot. Curve of complexity in nature.

Lorenz. Making order from chaos with simulations of global weather patterns.

The cavitons in plasma are measured in microns and microseconds. "They're also in the atmosphere, where they are meters big, and in the solar wind, where they can be kilometers big," Rose says. "What we're interested in is, once you excite them, how do they develop nonlinearly?"

A propitious time

What is remarkable about these paradigms of nonlinear science is that they came into their own almost at the same time. If one had to pick a year, 1975 would serve as well as any. It was then that James Yorke of the University of Maryland first used the word chaos to help describe natural phenomena and the year that Benoit Mandelbrot published his first book (in French) on fractals. Things rarely work so neatly, but the 1970s, in general, was a time when the scene was ripe for the discovery or rediscovery of techniques and concepts of importance in nonlinear science.

That period saw the emergence of mathematical methods to look at stability within nonlinear behavior. In his office at Berkeley, mathematician Jerrold Marsden recently gave a simple demonstration of two such systems. He opened a window so that the slats in a venetian blind began vibrating gently as the breeze blew over them. Then Marsden put a rubber band around a book and flipped it into the air.

The venetian blind in the breeze is an excited system, driven by the energy of the wind, he points out. The tossed book is a conservative system, with no energy flowing into it after the initial toss. The development of oscillations in the blind can be described mathematically by what is called the Poincaré/Andronov/Hopf bifurcation, developed in 1943 by Eberhardt Hopf, who then worked in Germany and later went to the University of Indiana. The Hopf bifurcation can also be applied to the oscillating behavior of the wings of an airplane in flight and to other systems that oscillate when excited, including many in chemistry and biology, Marsden says. An essential point is the demonstration that a nonlinear system can be stable under certain conditions, and under other conditions it can lose that stability to oscillations.

Other equations make the same point about other kinds of systems. If a book is tossed up on edge, Marsden says, it can be described as stable because it retains its initial rotary motion. The book may wobble but only slightly. But when the book is tossed up on its broad axis, it begins to wobble immediately, with motion that is unstable.

Mathematical systems

Several related mathematical methods can be used to describe the stability of nonlinear systems. One is the energy-Casimir method, named for Hendrik

Casimir, a noted twentieth-century Dutch-born physicist. The energy-Casimir method is an extension of classical energy techniques for studying the stability of systems such as rigid bodies. It looks for certain properties of motion, such as energy and momentum, that can be used to predict whether a system will drift beyond certain limits, possibly into chaotic behavior.

A second method, called the KAM theorem, gives more detailed information than the energy-Casimir technique but is applicable to fewer systems. Like the energy-Casimir method, the KAM theorem is similar to mathematical techniques developed in the nineteenth century to describe such problems as the stability of the solar system. Both methods are important in studies of the stability of plasma—a hot, completely ionized gas—in connection with fusion energy research.

In the early 1960s, Soviet mathematician Andrey N. Kolmogorov first conjectured the existence of doughnut shapes—bounded tori—that could be used to provide stability criteria for a nonlinear system. Vladimir Arnold, also working in the Soviet Union, proved the Kolmogorov conjecture in a paper published in 1966. The Swiss mathematician Jurgen Moser completed the trio by providing an independent proof. Hence the anagram KAM.

Besides plasma physics, the KAM technique is useful in a large number of systems—Saturn's rings and other celestial phenomena, the classic three-body problem among them. It finds some order in chaos. "What it says is that simultaneously with chaos, you can also have a nice description of some orbits," Marsden says. "If you draw a curve in a plane to delineate how the system moves with time, some regions are filled with nice, regular, periodic orbits and others with chaotic ones. KAM delineates those regions where the orbits are orderly."

A math upheaval

Thermodynamics may be changed slightly by nonlinear science, but mathematics may face an upheaval. Heinz-Otto Peitgen is one of those who believe that mathematics is in transition from one mode of thinking to another. On a cold, rainy day in Santa Cruz—weather all too reminiscent of the Bremen he left recently—Peitgen talked about how all the elements in nonlinear science have come together to cause the change and, in the course of the discussion, gave an eloquent description of the nature and appeal of experimental mathematics.

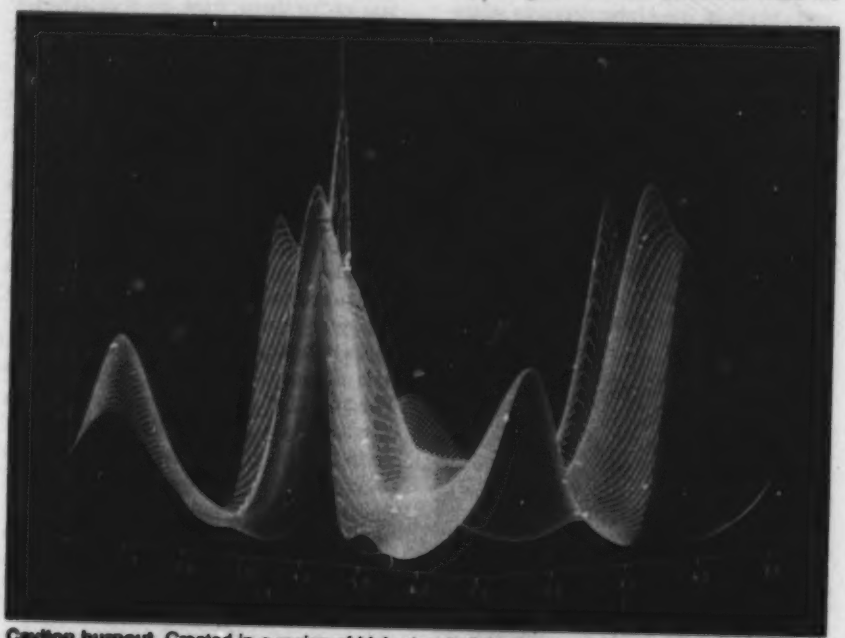
Marsden. Regular orbits and chaotic dots.

Take a typical nonlinear model problem, a particle in a plane that feels the effects of several different force fields, Peitgen says. Each force field has its basin of attraction. The point on the boundary between these force fields can be described typically as a fractal, Peitgen says.

In view of their incredible complexity, "the only way to get an intuition of what these boundaries are like at this time is to run computer-graphical experiments in which we picture the boundaries," Peitgen says. "How do these fractal basic boundaries change as one changes the parameters of the system? Typically, we see a sudden jump as parameters change. There is a bifurcation. What is the mechanism of this jump? Again, the only way to build an intuition about it is to run computer simulations."

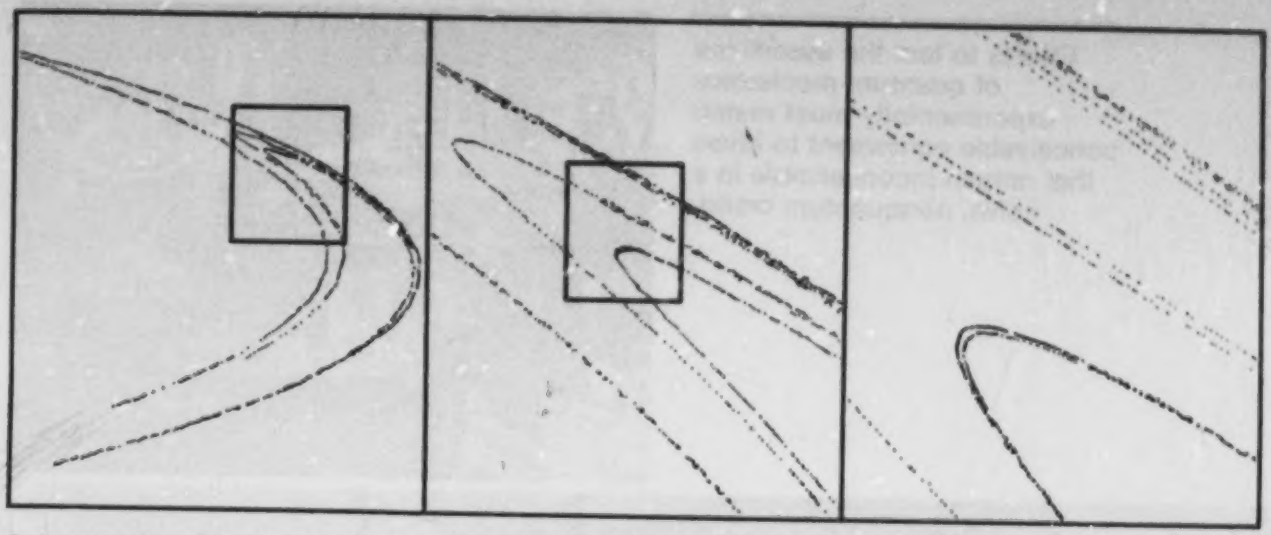
In broad outline, this procedure does not seem different from what mathematicians have always done, Peitgen says. It is common to intuit the answer to a complex problem, then do a pencil-and-paper test of the intuitive answer—in essence, an experiment—and finally to produce a rigorous proof of the solution. "But it has never been a major part of mathematics to do these experiments systematically, as we do now using the computer. That is new in mathematics, but it is typical to an experimental scientist.

"I find this very challenging, that mathematics is entering this domain," Peitgen says, "but there is a big dispute about whether this is really mathematics. Pure mathematicians say that we reject rigor, and that therefore what we



Caviton burnout. Created in a region of high electric-field density by high-energy beams, a caviton can quickly collapse, with the result that its energy is transferred to electrons.

Edelson is the author of "The Problem of Macrovariables," Mosaic Volume 17 Number 1.



Strange attractor. In a series of inserts, blowups show periodic equilibrium state of orbiting system moving with time. Marsden drew these graphics on a home Macintosh computer.

do is not really mathematics. I understand their concern. They see the traditional basis of mathematics, the requirement for rigorous proof, threatened, and they want to defend it. I don't think that what has been true in the past will be true in the future of mathematics. I believe that mathematicians will have to be satisfied in many cases of complex systems with experimentally gained insights rather than demanding rigorous proof, or they will have to leave important problems aside for a long time—maybe forever. Intellectually, this is a challenging way to go.

"The importance of computer graphics is the addition of the visual component to mathematics," Peitgen explains. "Never before have mathematicians been able to use their visual sense to understand a problem as now. Some critics challenge this method because they believe that mathematics is something that is carried out in the brain. I consider this view to be very limited. It is true of many branches of mathematics but not of the problems we investigate.

"Right now we are in a period of transition. We have traditional mathematicians who don't use the computer, who cannot write programs, who do not use graphics. And we have younger mathematicians, trained in computers, who are enthusiastic—perhaps too enthusiastic. In not more than ten years, all the considerations we are discussing will pass away because the new generation in mathematics will find the use of the computer and all its applications completely natural, and this will change the face and methods of mathematics in a revolutionary way."

Another change that traditionalists find equally unsettling is that the mathematician working on a nonlinear problem typically is part of a team. "In mathematics," Peitgen says, "traditionally you work by yourself. In academic evaluations, it is not good for your career if you publish too much with others. In experimental mathematics, more and more is team work. We work with scientists and with programmers who understand what the problem is. The more sophisticated the experiments become, the more you need teams of two or three or four persons working on it."

Fractal. Out of science and into art.

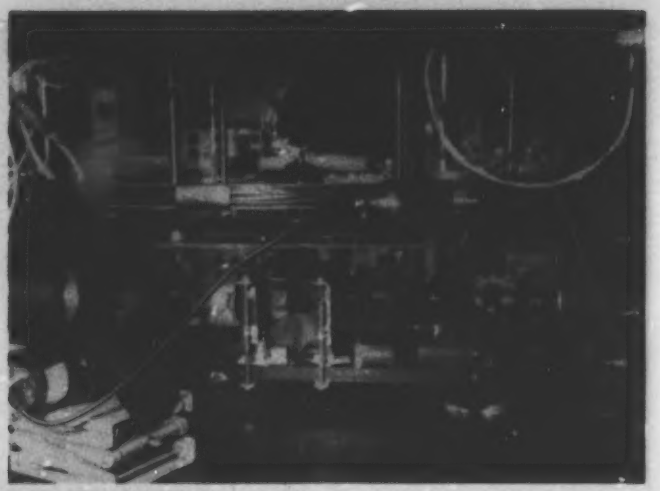
This aspect of nonlinear science causes skepticism in many quarters, David Campbell notes. "A lot of people, despite all the evidence, still consider the field flaky because it is interdisciplinary," he says. "Critics say it is dilettantism and that nonlinear physicists trying to do work in biology produce marginal biology. There is some truth to this. The most successful interactions involve two or three people, so experts can talk across disciplines."

Jerrold Marsden adds another point: "Substantial technology transfer between disciplines is a bit alien because it is relatively new—it is only fairly recently that there has been significant technology to transfer." Joseph Ford adds still another: "I can go to large meetings on nonlinear science now," he says. "When I started, there were only five people on the planet who understood enough to care." ●

Articles related to this one that have appeared in recent *Mosaics* include: "Fractal Symmetry" by Mort La Brecque and "Chaos: The Ultimate Asymmetry" by Arthur Fisher in Volume 16 Number 1; "Mathematicians at the Receiving End" by T. A. Heppenheimer in Volume 16 Number 4; "Many-body Problems" by Mort La Brecque in Volume 17 Number 1; and "Routes to Chaos" by T. A. Heppenheimer in Volume 17 Number 2.

The National Science Foundation contributes to the support of work discussed in this article through several programs in its divisions of Physics and Mathematical Sciences.

Efforts to test the assertions of quantum mechanics experimentally must match conceivable equipment to ideas that remain inconceivable in a naïve, nonquantum world.



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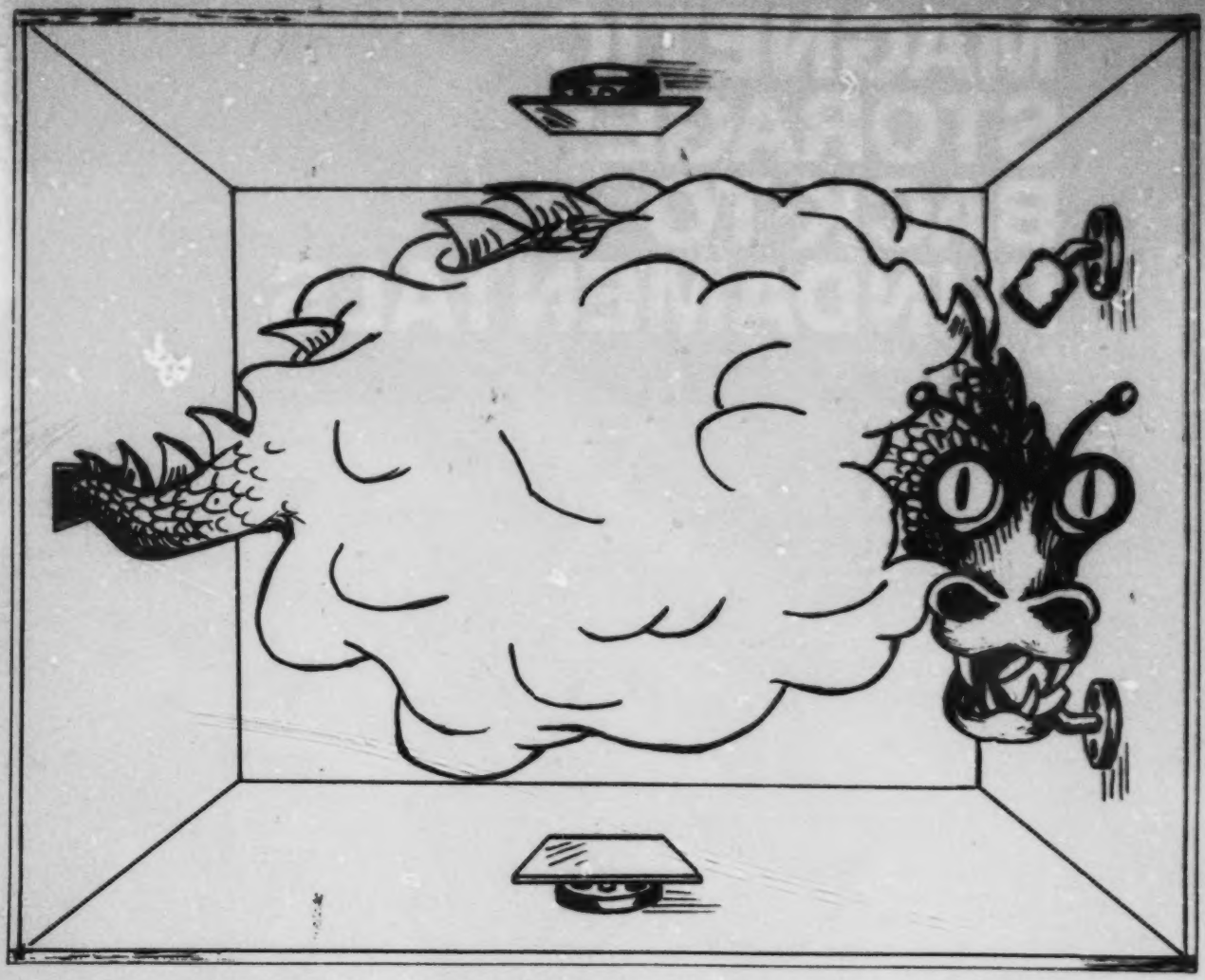


simple in the essentials, and it may become possible to build such equipment to conduct demonstrations in physics courses. One reason QM is unfamiliar is that students see few concrete examples that demonstrate its character. Although QM may remain strange to the layman, in time it may become as clear to the physics student as Newton's mechanics or Maxwell's electrodynamics.

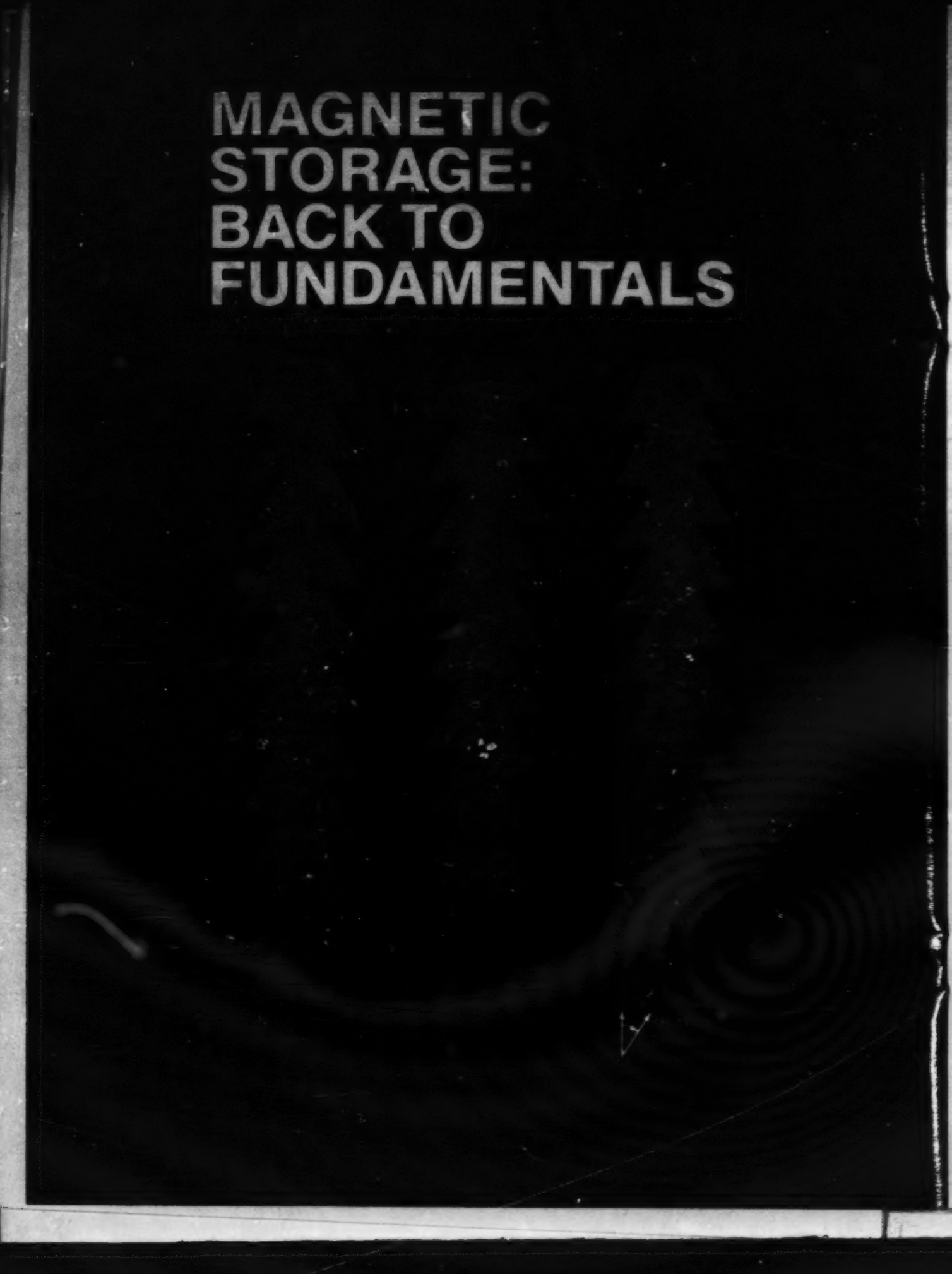
"Those who are not shocked when they come across quantum theory cannot possibly have understood it." This statement by Niels Bohr unconsciously echoed the preface of Copernicus's *De revolutionibus orbium coelestium* in 1543: "Many scientists, in view of the already widespread reputation of these new hypotheses, will doubtless be greatly shocked by the theories of this book." For that matter, Einstein's assertion that "God does not play dice" recalls the statement of Alfonso the Wise, king of Castile, after studying Ptolemy's geocentric system of astronomy: "Had I been present at the creation, I would have given some useful hints for the better ordering of the universe."

Wheeler and his dragon. A photon, says Wheeler (below), is a great smoky dragon, its tail clearly defined emerging from its source, its teeth sharp striking the detector. Everything between is smoky.

The assertions of QM are unfamiliar and appear paradoxical in the light of common experience. However, John Wheeler notes that the view of Gertrude Stein on modern art is appropriate: "It looks strange and it looks strange and it looks very strange; and then suddenly it doesn't look strange at all and you can't understand what made it look strange in the first place." In Wheeler's view, the assertions of quantum mechanics in time will become as well accepted as those of Copernicus. •

The National Science Foundation contributes to the support of research discussed in this article principally through its Theoretical Physics Program.

MAGNETIC STORAGE: BACK TO FUNDAMENTALS



Long driven by engineering necessities, magnetic storage technologies are drawing the attention of academic and other fundamental investigators in the United States.

Until recently magnetic recording tended to be seen as the dull side of computing—absolutely essential, but seemingly not very interesting as a research topic. As a consequence, although computer architectures, chip design, and new semiconductor materials are entrenched in academic research, work on magnetic data storage has until recently been invisible in the universities. It is difficult to find any fundamental research advances in data storage—except if Japan is included—that come close to the seminal work being done in the United States in computer science and engineering.

The binary digits that are the feedstock of computers are stored as magnetic bits on tape or disk. Disks can be either flexible (floppies) or rigid or fixed (Winchesters). Whatever the disk form, the objective is to obtain greater data density in ever smaller devices and faster access to and retrieval of that data. The most telling of these characteristics is data density; for rigid-disk files, this measure has doubled 11 times in the past 28 years. This doubling has been achieved not through fundamental research but by precision engineering, applied mainly to the narrowing of the gap between the recording head and recording medium. The engineering has been abetted by some Edisonian improvements in the recording materials, but nothing spectacular.

That history of engineering, driving exponential improvements in data densities—may be changing. This is evidenced by the recent establishment at several universities of centers of varying sizes and agendas to perform research on magnetic storage of information. Funded almost exclusively by industry, these centers are at Carnegie Mellon University, the University of California at San Diego, the University of Santa Clara, and the University of Minnesota.

With the growing Japanese dominance of the magnetic recording market, the sudden emergence of these centers points to a sense of urgency. Why, then, these centers? One reason is that although fundamental limits are still far away, practical limits are apparent. The fact is that the increases in the density of stored data show every sign of continuing, with the fundamental density limit still about two orders of magnitude away.

What partly dispelled the comfort brought by past increases in storage densities, according to Albert Hoagland of the University of Santa Clara, was a nine-month delay by IBM in the release of its 3380 disk file for mainframe computers, currently the state of the art in disk storage. "That," he says, "telegraphed to the industry that the technology was moving on to a new level of sophistication, and it's not just turn the crank anymore."

The practical limits that now have to be dealt with include the submicron size of the magnetic bit, a dimension at which surface properties begin to dominate. Further, at submicron ranges, the information can be more easily lost through demagnetization, and ways to raise the activation barrier—the coercivity, or field needed to force a magnetic transition—must be found. There are such ways, but they are limited and not well understood. A second limit to substantial progress is the physical spacing between the recording head and recording medium—now less than the wavelength of light.

The smaller the spacing, the greater the resolution of the readout and the greater the density with which magnetic bits can be packed. Of course, the head and medium can be run in contact, as is now done for the flexible disk and tape, but that is not an option for the rigid disk, in which the aerodynamically contoured head literally flies over the disk. And although Winchester technology is being pushed further, limits will be reached at some point. Indeed, the engineering already done is astounding: A flying Winchester head has been likened to a 747 passenger jet flying at 800 kilometers per hour at one-quarter of a centimeter above the ground.

There are several ways to attack these practical limits. One, of course, is to push the engineering further. Another is to change the recording medium, from the present-day particulate media to thin films. Such films, offering higher bit densities, have a thickness of about one-tenth the wavelength of light, but they are laden with corrosion. Particulate media, for now the almost universal choice, consist of submicroscopic particles—since 1934, usually iron oxides—mixed into plastic binders. The combination is painted on a substrate to become tape or disks. Thin films, by con-

Memory storage. In creating memory on a thin garnet disk, magnetic bubbles are driven by a rotating magnetic field around patterns that are masked from ion bombardment.

trast, are made with ferromagnetic metals and alloys.

Yet another alternative is to change the technology. One possibility is magneto-optical recording, which blends the read and write abilities of magnetic recording with the extraordinary densities of optical recording. Another possibility is a new generation of magnetic bubble devices, which would incorporate schemes for multiplying information densities and for endowing the devices with the information-processing abilities of semiconductors.

These various alternatives are somewhat exclusive—complementary rather than competitive—although in some instances, such as magneto-optical recording, one technology may indeed crowd out another. The point, says Mark Kryder of Carnegie Mellon University, is that "we have a whole slew of new technologies that are making it possible to extend the straight-line increases in recording densities for rigid disk files. Making the right choices is crucial."

Convergence

The research now under way is diverse, but it is bonded by some underlying convictions. One is that the current fashion for multidisciplinary research truly applies to the search for higher densities and new recording technologies. As Albert Hoagland says, "Semiconductor and microelectronics can be put in the double-E department at Stanford, but this business is so interdisciplinary that the talent you want may be off in some strange department that's never heard of a disk file."

A second conviction is that ultimately the storage densities of magnetic and optical recording will converge. To follow the logic it is necessary to appreciate that density is assessed in two ways: by linear density, or number of bits per unit length laid down a track, and by track density, or number of tracks per unit length. Optical track densities are much narrower than those of magnetic recording, but the belief is that this difference will narrow and with it the density advantages now held by optical recording. As John Mallinson of the University of California at San Diego says, "The track width for mainframe computer disk files has barely changed in the past decade. It was 960 tracks per inch then and it is 1,125 now."

A third conviction is that near-term advances will depend in the main on

Kryder. A whole slew of new technologies.

bravura engineering and that leaps toward fundamental limits will necessarily depend on some insights into the recording process itself.

For the long term, there is a battery of puzzles. One is the capacity of a recording channel. How much information can it in fact hold? "Are you at 10 percent of capacity? Are you at 90 percent?" asks Jack Wolf of the University of California at San Diego.

Wolf's route to the question is by way of information theory, which was initially created for communications networks but is also applicable to recording. As Mallinson points out, like a communications network, a magnetic recording channel "has a limited bandwidth, has distortion, and suffers from nonlinearities, errors, fades, dropouts—the whole gamut of things that occur in the telephone channel or satellite communications." Where they do differ is in the fact that the capacities of telephone and other communication channels are calculable, but those of recording channels are not, because in recording channels there is a limit—a peak amplitude constraint—on the sort of signals that can be imposed. "Surprisingly," says Wolf, "with a peak-amplitude constraint, we don't know what the capacity is. It's beyond our ability to carry out the calculations."

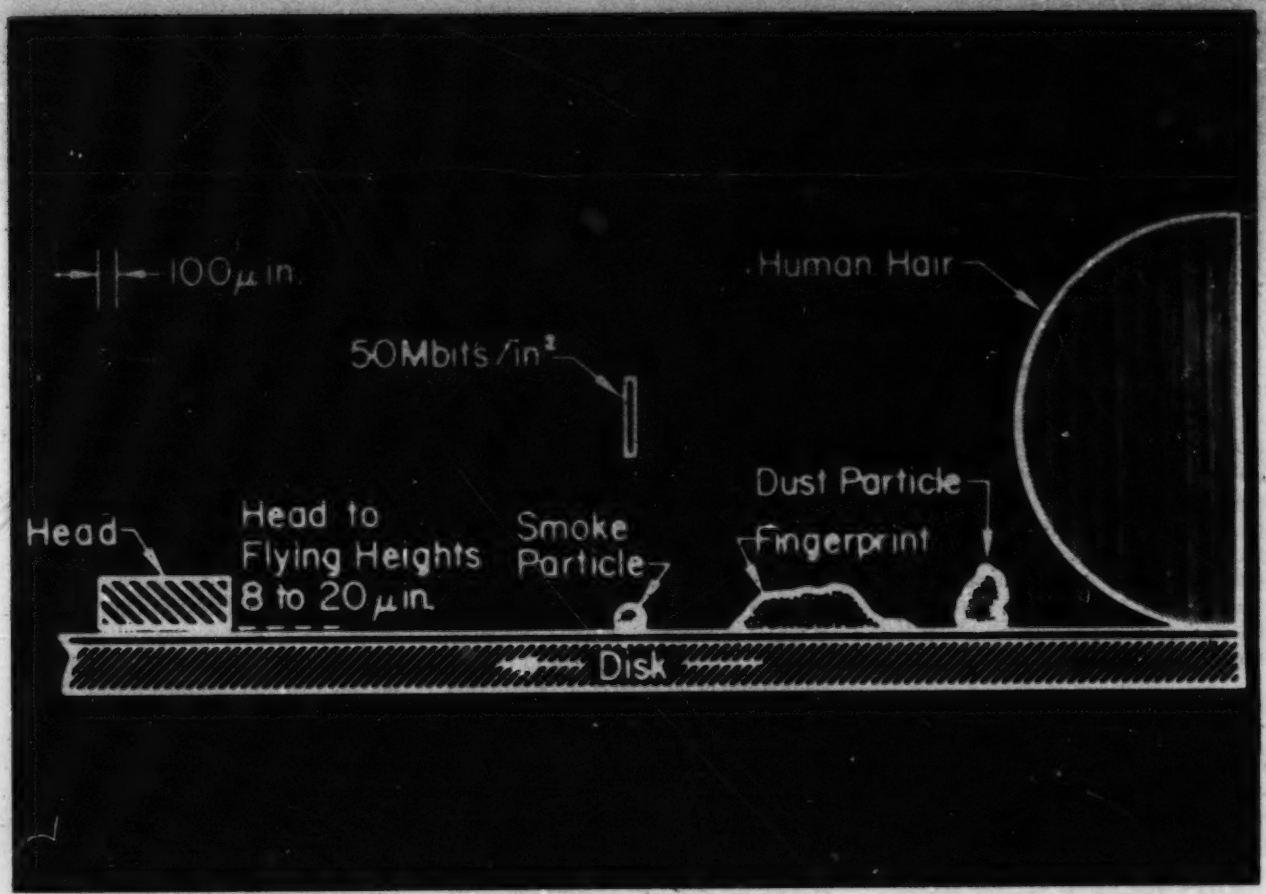
Charap. Then something funny happens.

Wolf, noting that "while the channel, to a communications theorist, is the part of the system you can't change, with magnetic recording there seems to be nothing that you can't change," is framing recording as a blank tablet. "If I were to start from zero, how would I design a system? That approach will probably give us the big gains. But I don't know how to do it."

One tack is to reform the coding of information. Two kinds of code are used to store bits: error-correcting codes, to make up for bit losses or errors, and modulation codes, which time the reading of the information. Wolf says, "I would not treat error-correcting codes differently from modulation coding. I would find a unified code that accomplishes both tasks."

Concurrently, Wolf intends to look at decoding methods. He is especially interested in soft-decision coding, which is used in communications and which delays decoding until there is reasonable certainty that the decoding decision is right. In particular he is looking at Viterbi decoding, devised for communication channels by Andrew Viterbi, a San Diego colleague. "It's called soft-decision decoding," Wolf explains, "because you're not just using the one or zero aspect of what you're reading, but more of a quality measure. It gives you maximum-likelihood decoding."

Wolf's efforts to understand channel capacities are being bookended by those of two of his San Diego colleagues, H. Neal Bertram and Sheldon Schultz, who seek to understand what happens in the actual act of recording. "We want to fundamentally understand the recording process," Bertram says. "If I change a single parameter, what does that do to my signal-to-noise ratio? How important is the grain size? The coercivity?



Dimensions compared. The size of a high-performance flying head of a Winchester disk drive is compared to familiar objects like dust, fingerprints, and hair, which dwarf it.

The magnetization? Are vertical media better or worse than longitudinal media? These things are understood approximately, but the details are not understood. It's too hard a problem mathematically. It's a nonlinear, two-dimensional problem of an interacting system. You have got particles, grains, that interact with magnetostatic energy. It involves long-range interactions."

Flip and chaos

There is agreement that a magnetic particle transiting from one polarity to another, from on to off or from one to zero, does not just flip. There are models—variously buckling, chain, curling, and so forth—of what does happen. All of them work, or can be made to work, with the right conditions. None of them are universal.

A recent idea being looked at by Sheldon Schultz is that the transition from one magnetic state to another is a chaotic one, subject to the mathematics of chaos theory. "It's already been shown in the laboratory," Schultz says, "that if you take an ideal ferromagnetic system and start hitting it with microwaves, you can make it illustrate many of the features found in chaotic motion." However, as Stanley H. Charap of Carnegie Mellon says, "the thing about a magnetic system is that you may get on the route to chaos, but then something funny happens: Things are becoming chaotic, but then suddenly the magnetization finds itself in an entirely new situation. Since it's mostly in the direction of the applied magnetic field, it's no longer driven by it. Chaos dies away." (See "Chaos: the Ultimate Asymmetry" by Arthur Fisher, *Mosaic* Volume 16 Number 1, and "Routes to Chaos" by T. A. Heppenheimer, *Mosaic* Volume 17 Number 2.)

These are the global issues of magnetic recording. Beyond them, in reaching for narrower spacing between head and medium or smaller bit sizes or greater packing densities, researchers move to what Albert Hoagland calls the cutting issues of better engineering, chemistry, signal-processing techniques, tribology, materials, and surface science.

Magnets and lasers

Magneto-optical recording illustrates the point: Although products using this technology are nearing the market, the technology still faces formidable materials problems.

In magneto-optical recording, a laser is used to both write and read, simplifying the process mechanically and allowing for closer track spacing and hence much higher densities. The storage is magnetic, so that the hybrid moots the read-only blindness of optical storage of digital data. Magneto-optical writing takes advantage of the fact that laser heating momentarily lowers coercivity, while the reading depends on the Kerr effect, the rotation of a plane of polarized light by a magnetic field.

The most promising magneto-optical materials are thin films, formed of rare earths and transition metals by sputtering metals off an electrode and onto the

film. The typical magneto-optical film, John Mallinson says, is a 100-angstrom-thick layer of iron terbium cobalt; some films, though, are gadolinium iron cobalt. "The present trouble with magneto-optical films is that terbium, which is the favorite one, is highly reactive to oxygen," he says, "but in oxidizing, the magneto-optic signal is lost." However, Mark Kryder believes that "if you look at the signal-to-noise ratio that people are obtaining now, it is adequate for obtaining error-corrected signals which are good enough for computer applications at data rates comparable to what Winchesters operate at today. You could take today's materials, and if you are 100 percent certain of corrosion resistance, you've got a product. That's probably the outstanding thing holding back the technology from implementation: convincing yourself that a material that has rare earths in it and is only a few hundred angstroms thick will last for 10 years."

Hoagland. Disk-storage technology is moving to new levels of sophistication.

An Achilles' heel

Conventional recording—pure magnetic recording—shares the problems of the durability of thin films. This is not to say that current recording media—relatively thick tapes—are played out. As Albert Hoagland says, "You can still gain a lot of density by staying with particulates." And as Stanley Charap says, present-day recording technology "at the simplest level is guaranteed to work." Yet the obdurate fact is that increases in recording density have been paced by a reduction in the recording gap, that this gap is now close to zero, and that further increases in the recording densities of rigid disk files are most likely to come from the use of thin films.

Why? Because the writing surface needs to be as close as possible to the gap. "You want to do the writing, the recording operation," says John Mallinson, "in a very high field gradient. And the only place you get very high field gradients are very close to the gaps and the heads—that's the small, narrow nib in your pen. So you want to get the recording very close to the gap. If you back off a very long distance from the gap," says Mallinson, "then you don't get very high field gradients. So for both writing and reading, you want to be very close to the medium. You prefer it to be thin film, and that's the Achilles' heel of recording: the necessity for operating in very, very close proximity."

Thin films are the Achilles' heel because their use wipes out the latitude inherent in the conventional and much thicker recording tape—and disks. Bumps and other defects on tape or disk become mountains in thin films; the ability to lodge lubricants within thick films is lost in the thinner ones, and the varied puzzles involving surface effects, which could formerly be ignored, must now be dealt with.

Thus, as Glenn Sinclair of Carnegie Mellon points out, no disk can be made perfectly smooth, and "when you talk about very thin layers, those disparities could be as much as 10 percent of the height of the layer. So when you're trying to model bearing wear, for instance, you have to model it as point contact rather than intimate contact over the whole surface."

Mallinson. Thin film is the Achilles' heel.

The formulation for conventional recording tape and disks includes lubricants, which endure for the medium's lifetime. "But," says Mallinson, "there is no way that you can incorporate the lubricant in the metallic thin film. Somehow you have got to put on a topical lubricant that lasts for the lifetime of the tape or disk." Current candidates are fluorinated oils, sputtered silicon dioxide layers, and sputtered carbon layers.

Thin films also make surface a dominant issue, and that raises a litany of puzzles. Japanese engineers found several years ago that soaking ferric oxide particles in a cobalt solution doubled their coercivity, improving their recording characteristics. Why this is so is not known, despite vigorous application of various surface analytical methods. "It's known," Mallinson says, "that the cobalt is only resident in the outer 30-angstrom layer of the material. It's also known that if you diffuse the cobalt all the way into the particle, the coercive force becomes temperature dependent and stress dependent. If you just have the cobalt on the surface, the increase in coercive force is relatively independent of temperature and mechanical stress. It's not known why."

Similarly, dousing iron oxide particles in sodium metabisulfite reversibly raises their coercivity threefold. Again, it is not known why, despite some heroic applications of surface analysis. That is not simply an interesting academic puzzle, for researchers would like to attain these higher coercivities in a fashion that does not compromise other recording characteristics, and they

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Metzger is the author of "Taunting the Computer," Mosaic Volume 17 Number 1.

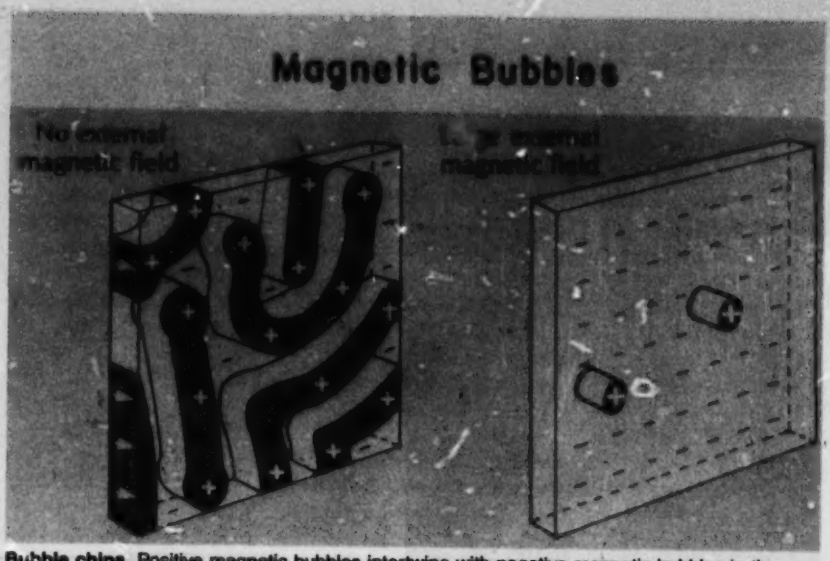
would prefer to do so from first principles rather than simply by running through the reagents in the chemical supply room.

Pitch and yaw

Thin films represent one dimension—arguably, the most important—of the drive to increase recording densities by closing the gap between the head and the medium. A complementary approach is to find ways to bring the flying heads of Winchester systems even closer, and, improbably, to operate them in actual contact. As Albert Hoagland says, "The desire for density and the consequent pressure to move toward true contact is immense."

What lower limit on the flying head is feasible? In a Winchester system, Hoagland says, the "head mount is being accelerated with tremendous g forces and stopped to be on track. It's like an airplane. You've got to stabilize it; it's subject to pitch and yaw. And what you can do is a function of how smooth you can make the medium, a function of materials selection between the head and medium, a function of design and a good assembly. That's where the leverage for a lot of advances resides."

Operating a flying head moving at relative speeds of hundreds of kilometers per hour at less-than-wavelength spacing above a hard disk melds mechanics and atomic physics, macroscopic and atomic properties, says Theodore Geballe of Stanford University. "A crack is a macroscopic quantity and a vacancy is an atomic property," he adds. "When you start getting vacancies together, you end up with a crack."



Bubble chips. Positive magnetic bubbles intertwine with negative magnetic bubbles in the absence of an external magnetic field (left), but shrink when they are in a negative field (right).

The researcher also ends up with assumptions about wear that work in, say, modeling wear trends on a four-lane highway, but not in the submicroworld of recording. For example, stress-strain curves are usually the same for different sizes, or scales, of the same material. In thin films, however, layers some 400 atoms thick are being sampled; and here, Glenn Sinclair says, "you start to question the averaging that's implicit in continuum mechanics."

Geballe. Mechanics and atomic physics.

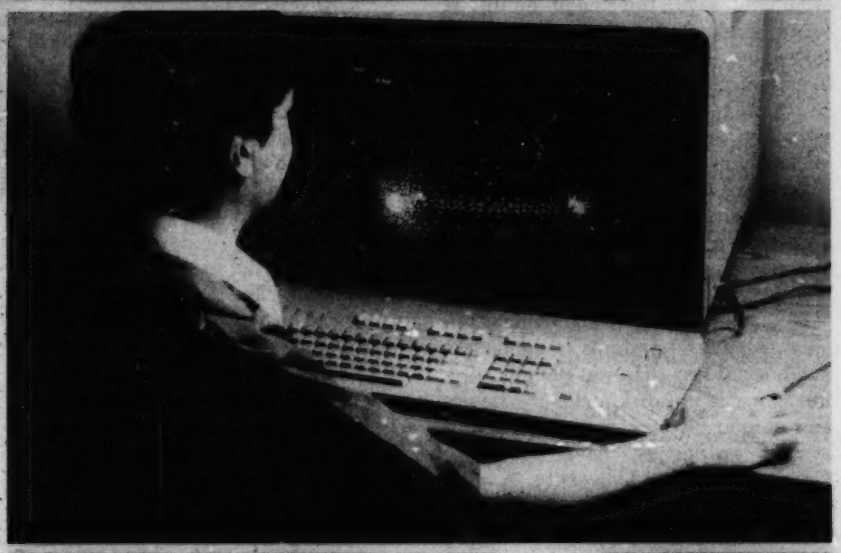
Good news and bad

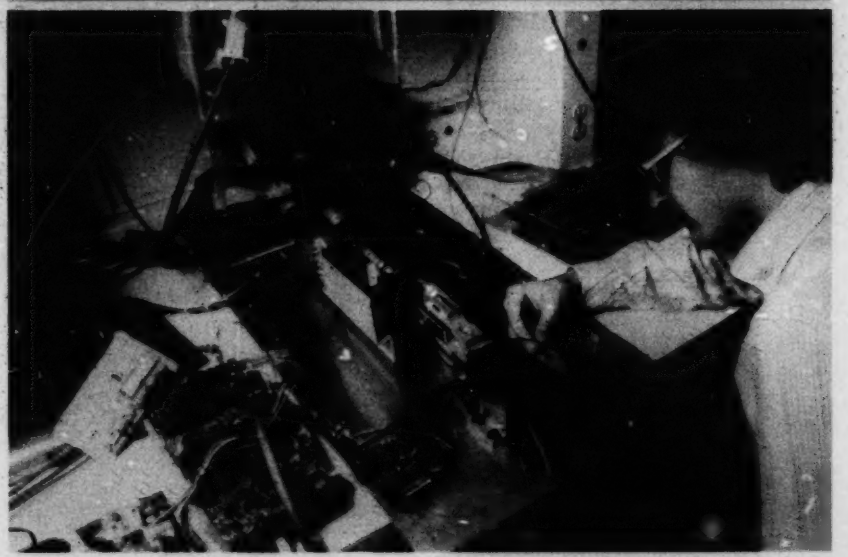
Just as there are two sorts of recording media, the standard particulate and the newer thin films, so there are two ways of recording—longitudinal and vertical. In longitudinal recording, used exclusively in conventional recording, the plane of magnetization is parallel to the plane of the recording tape or disk; in vertical recording, the plane is orthogonal.

Vertical recording is an old idea, resuscitated in the 1970s by Japanese engineers who found that certain materials, principally alloys of cobalt and chrome, favored vertical recording. The idea is now being pursued because it seems to be an alternative or a complement to thin films in raising recording densities. That is, it offers higher bit densities—higher anistropies, or preferred direction of recording—than longitudinal recording. As Mark Kryder and Alfred Bortz of Carnegie Mellon have written, "In vertical recording the transitions between adjacent magnetic domains of opposite orientations don't tend to increase in size, as they do in longitudinal recording."

It is possible to argue whether these higher densities are more alluring than realistic. Albert Hoagland takes the position that "it's gotten a lot of hype. It's just magnetic recording, just a different orientation of magnetization. So, the same loss factors apply." Kryder, who is more accepting, says, "Vertical recording does allow you to obtain a

Sinclair. Queries on 400-atom-thick layers.





Ph.D candidates. (Clockwise from top left): Philip Mitchell peers at ferromagnetic resources spectrometer; Robert Uber fashions magneto-optical recording system; David Shenton studies behavior of magnetic recording head; Mark Schultz demonstrates his high-speed actuator.

higher bit density in the medium than one can obtain with longitudinal recording. But in order to write very small bits into the medium, you must get the head very close to the medium. And if you can't fly closer with the vertical recording than you do with longitudinal recording, then you don't get any advantage." The issue is like reading a newspaper from 20 feet away; a slight difference in type size is irrelevant.

The upshot is that the density advantages of vertical recording are being explored for tape and flexible disk media where the head is in direct contact, with barium ferrites at the moment being the most promising materials. "The problem," says Kryder, "is that barium ferrite particles are little, disklike particles, like poker chips." In their fabrication, these chips stack, leading to signal-to-noise losses. "So," says Kryder, "the issue is making small particles uniform in size and evenly dispersed through the medium. If that problem can be solved, then you'll see vertical recording, at least in contact recording systems."

Bubbles, stripes, and lines

Otherwise-random magnetic domains can be aligned in crystalline garnet into cylinders of up/down magnetism—bubbles. A bubble can denote an on-gate, or one, to a computer and its absence can denote an off-gate, or zero. And a bubble chip—a solid-state device, unlike a Winchester disk but like a semiconductor chip—can be both a passive data store and an internal memory for a computer, acting (in effect) like RAM, random access memory. Because bubble structure depends on a permanent magnetic field, information is kept even when power is lost; RAM memory, of course, is lost. Moreover, bubble chips—made of permalloy, a nickel-iron alloy, lithographed on garnet film—are extremely durable under extreme conditions of temperature, vibration, radiation, and the like.

However, data must be retrieved from bubble chips sequentially, making bubble memories considerably slower than semiconductor memories. Although there are novel ways to speed up access, the issue endures, as does the fact that bubble storage remains more costly than conventional data storage on tape or disks. "If bubble density can come up high enough," Mark Kryder says, "then I think it becomes more than just a niche for high-reliability, nonvolatile storage."

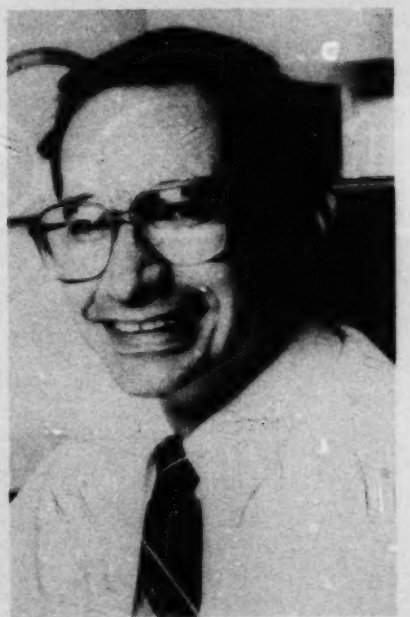
There are now two principal ways to raise bubble densities, one more arcane than the other. The first, dating back to 1972 and now in the developmental stage, uses ion-implanted contiguous disk devices. The second, reported in 1983 and still more an idea than a device, uses vertical Bloch line memories.

The first approach, which is aimed at multiplying the current bit densities of bubble chips up to 16 times, combines ion implantation to modulate the magnetic properties of garnets with lithographic techniques of the semiconductor industry. Says Kryder, "If I can do one-micron lithography, which is routine today, I can make a two-by-two-micron bit cell, which works out to be more than 16 megabits per square centimeter. We'll have it first in Japan and France, then in the United States."

These numbers, though, pale before the alluring promise of vertical Bloch line memories, in which the scale is not millions but billions of bits per square centimeter, offering the highest storage densities of existing and even conceivable storage technologies.

Humphrey. Pursuing phenomonal densities.

If the magnetic field imposed on a bubble chip is lowered, the bubbles reform into stripe domains of up-and-down magnetization. The domain wall is a transition zone between magnetic domains. This transition zone, one of twisted magnetization, is the Bloch wall, named for Felix Bloch, who identified it in the 1930s. And the essence of vertical Bloch line memories is to move information from bubbles into lines resident in the Bloch walls. These lines can be written with much smaller spacings than bubble dimensions, thereby multiplying information density enormously.



Bortz. Vision of magnetic bubble memories.

"Their presence or absence," says Kryder, "can now represent data rather than the original bubble itself. We write and read with bubbles, but we store with vertical Bloch line memories. That gives us these phenomenal densities."

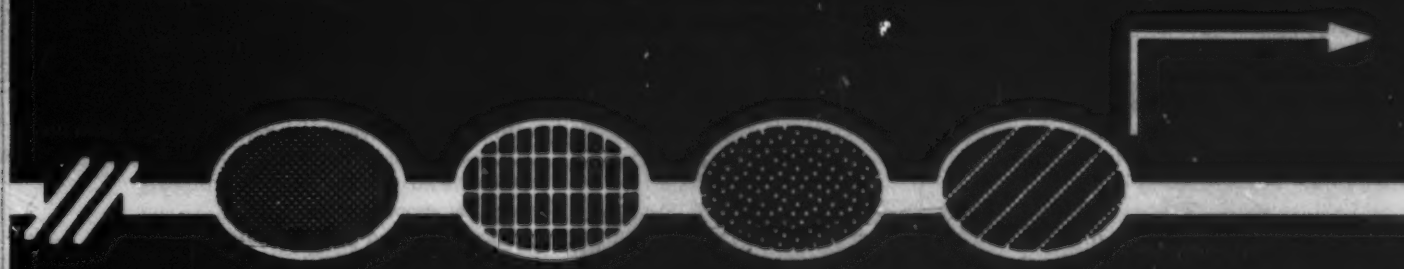
The idea comes from Susumu Konishi, at Kyushu University, and is being energetically pursued at various sites, such as the Nippon Electric Company, and by Floyd Humphrey and associates at Carnegie Mellon. And the leitmotif of research in other arenas of magnetic recording, the conjunction of multiple disciplines, applies to Bloch line memories. According to a National Research Council report on magnetic materials: "To make this highly attractive technology a reality will require the work of physicists to understand the dynamic properties of Bloch lines in bubble domain walls, the work of engineers in designing device structures to control and manipulate the Bloch lines, and the work of materials scientists to develop the optimum materials for this application."

The efforts to multiply bubble densities is on a track with parallel work to raise the information-processing capabilities of bubble chips, to have the chips serve as logic devices. There are two approaches: current-access and silicon-on-garnet. The current-access approach involves work by AT&T Bell Laboratories' Andrew Bobeck, who invented the bubble technology, and by Stanley Charap of Carnegie Mellon. It uses a relatively new technique, called current-access, for propagating bubbles in order to implement logic functions, with the repulsive interaction of two bubble streams, one carrying control bubbles and the other data bubbles, doing the work.

The silicon-on-garnet approach to logical bubble chips has as its hoped-for endpoint putting a microprocessor on a garnet chip, combining processing with enormous data storage. The vision, Mark Kryder and Alfred Bortz have written, is of "single-chip silicon-on-garnet computers with magnetic bubble memories in the garnet and logic and control functions laid out on laser-annealed polysilicon by VLSI [very-large-scale integration] techniques." ●

The National Science Foundation contributes to the support of research discussed in this article through its engineering research and materials sciences programs.

GENE ENHANCERS



DNA sequences that act on eucaryotic genes from great distances, regardless of their positions within the genomes, play a significant role in the regulation and control of gene function.

"Think small, talk big," an axiom dear to the hearts of molecular biologists, applies to the research model that has long guided efforts to unravel the mystery of how genes work. The axiom says that what is learned about gene regulation—about the way genes are turned on and off—in simple microorganisms applies just as well to far more complex life forms, including humans.

Initial studies centered largely on procaryotic, or anucleate, cells such as *E. coli* bacteria. In procaryotes, the molecules of heredity, the DNA, reside in the cytoplasm. More recently, in the wake of new advances in recombinant gene-probing techniques, considerably more attention has been given to viruses that invade the eucaryotic, or nucleated, cells of higher organisms. Out of this newer research has come a wholly unexpected discovery: the existence of control elements never observed in the repertoire of procaryotes.

These novel regulatory elements, consisting of short, discrete stretches of DNA, have been named gene enhancers. They act to turn genes on or substantially increase their activity. What surprised researchers about the new discovery is not only the enhancers' effectiveness—they can multiply gene activity 100 to 1,000 times—but also their most uncommon operating flexibility, compared to such other gene-regulating DNA fragments as promoters.

Promoters provide the signals that get genes going. When on (or derepressed, as the molecular biologists would say), they allow enzymes, RNA polymereses, to gain access to one strand in a DNA double helix and to copy the information encoded on the genes as a complementary strand of messenger RNA. The mRNA, in turn, directs the synthesis of the protein specified by the gene. Promoters are found just a short, well-defined distance upstream from where the genes they regulate begin. (*Upstream* characterizes sites that precede the origin of gene transcription—the so-called 5′ end of a protein-coding sequence; *downstream* is the region lying beyond the terminating, or 3′, end.)

Unlike promoters, enhancers function well whether located on the upstream or downstream side of an active gene, and they can act at a considerable distance from the gene-adjacent promoters upon which they exert their influence. Moreover, unlike the promoter sequences, which generally work only in one direction, enhancers can be flipped, the orientation of their sequences reversed, without a major loss in function.

Studies in growing abundance now focus on the mechanism by which enhancers, in conjunction with promoters, act on genes to step up the genes' mRNA output, their transcriptional efficiency. Investigators have come to believe that these studies will go a long way toward helping them unravel one of biology's greatest mysteries: cell specialization, cell differentiation. How is it that a single, fertilized egg ultimately gives rise to heart, liver, eye, brain, and kidney cells? Why do different types of cells produce different proteins, even though all cells in the body have identical genes? How are certain genes turned on in one kind of cell and other genes in another?

Gene enhancers, triggered into action by cell-specific proteins, may well hold the key to a big part of the mystery. Of more immediate practical potential, studies of the enhancers will probably lead to the development of more effective strategies for gene therapy. These studies are also expected to help provide a deeper understanding of many diseases, certain cancers and diabetes among them, that as George Khoury of the National Cancer Institute says, "are specific for specific tissues and clearly dependent on gene-specific expression."

A prototype

The discovery of enhancers came in 1981 from studies of a monkey tumor virus, SV40 (SV stands for simian virus). The virus SV40 consists of a small ring of double-stranded DNA that codes for six proteins, two of which are produced in the early stages of infection when the virus first enters the cell. In probing the control region of the virus, that stretch of the 5,243-base-pair ring not transcribed into mRNA, Pierre Chambon and his colleagues at France's University of Strasbourg and, independently, George Khoury and his associates at NCI, made similar discoveries. They identified a

side-by-side repeat sequence, 72 base pairs in length, as being critical to the expression of SV40's early proteins. Deleting this repeat unit, they found, served to reduce early transcription 100-fold and more, all but killing the virus. (The 72-base-pair repeats lay immediately adjacent to a sequence of three 21-base-pair repeats that represent one element of the promoters for both the early and late genes.)

Later in 1981, Walter Schaffner and his co-workers at the University of Zurich reported linking the SV40 72-base-pair repeat segment to a foreign gene, cloned from a rabbit, that coded for the protein beta globin, which is a constituent of red blood cells. Upon introducing these spliced ensembles into mouse cells, the Zurich group detected significantly enhanced gene expression. They showed further that the tandem repeats boosted transcription even when inserted thousands of base pairs away from the test gene's promoter. Chambon reported similar results with the gene for conalbumin, another animal-cell protein.

According to Khoury and others, however, full appreciation of the unique elements that these tandem repeats represented really came in a talk presented by Nobelist Paul Berg of Stanford University at a meeting held in the winter of 1981 in Keystone, Colorado. "What he had to report was outstanding," Khoury recalls, "because he spoke of essential features of these enhancer elements that none of the rest of us knew at the time." Berg told of experiments on SV40, conducted with Michael Fromm, in which the enhancer element was moved from the 5' (upstream) end of the gene, where transcription begins, to the 3' (downstream) end, where it terminates, without any reduction in gene expression. Nor did insertion of the tandem repeat with its orientation reversed, its sequences flipped, diminish enhancer influence. Thus did position independence and orientation independence become attributes that defined an enhancer element.

Action at a distance became another defining attribute, but how far was far? Some studies of recombinant DNA had suggested that enhancers could make their presence felt despite as many as 10,000 intervening base-pairs between them and the promoter adjacent to the gene being assayed. Other studies argued for a far shorter sphere of influ-

Khoury. Certain viruses from cellular DNA.

ence. The present view, based on more recent, rigorously defined experiments by Berg and his colleagues, is that it is not so much the distance between enhancer and promoter as what is in between. Certain sequences—another promoter inserted between the two, for example—will sharply curtail the effect. With that goes the presumption that an enhancer will have its greatest influence on the promoter lying closest to it.

Finding enhancers

Not long after the delineation of the prototype SV40 enhancer, a host of other enhancer sequences was being uncovered in numerous other species of animal virus, both DNA and tumor-causing RNA viruses. In the latter, the so-called retrovirus, the viral genome consists of a strand of RNA. Upon invasion of a eucaryotic cell, the RNA is transcribed, by way of the enzyme reverse transcriptase, into double-stranded DNA. This so-called proviral DNA is then incorporated into the chromosomes, where a stretch at each end of the DNA strand is duplicated. It was within these so-called long terminal repeats that the enhancers, along with the promoters and other transcriptional control sequences, were first found in retroviruses. The viral enhancer elements discovered to date generally are found frequently to consist of tandem repeats of between 50 and perhaps 200 base pairs. Scientists still are unable to explain the purpose of the repeats, since viruses with just a single copy of such a sequence have been found to be fully active, at least in the laboratory.

The prevalence of viral enhancing sequences intensified the search for natural enhancers in the genome, the genetic fabric, of eucaryotic cells. Scientists had good reason to think enhancers in cellular genomes were there to be found. For one, George Khoury explains, certain viruses—the small DNA viruses such as SV40, for instance—almost certainly arose from cellular DNA and therefore would have borrowed some control elements to facilitate infiltration and usurpation of target cells. This premise certainly seemed to be supported by the experiments showing virus-derived enhancers to be capable of stepping up the transcriptional efficiency in genes of a variety of cell types (not just rabbit beta globin and conalbumin but genes from mouse and chick as well).

One way to search, of course, would be to look for stretches of a cellular genome that showed homology, that is, base-to-base matching with known viral enhancers. There a drawback to this approach, however; rather than being like each other, the known viral enhancers show gross disparity in their nucleotide sequences. Enhancer elements from several viruses nonetheless do share a set of sequences, so-called core or consensus sequences, that appear to be essential to enhancer function. Using these as a guide, scientists at several laboratories identified possible enhancer regions in human and animal cells.

It was still necessary to demonstrate that identified enhancer sequences, plus others considered to be likely candidates for still other reasons, would actually enhance gene transcription. In the summer of 1983, three research teams—Walter Schaffner's in Zurich, and two at the Massachusetts Institute of Technology (one headed by Susumu Tonegawa, the other by David Baltimore)—independently provided clear-cut evidence that cellular genomes do indeed contain enhancers. Each team succeeded in demonstrating transcriptional enhancement using sequences discovered in association with the immunoglobulin genes of active B-lymphocytes, the cells that produce disease-fighting antibodies. (In these cases the enhancing elements were discovered to be situated neither on the 3' end nor 5' end but in the middle of the gene.) Not

long afterwards, William Rutter and his colleagues at the University of California at San Francisco identified an active enhancing sequence found in affilitation with the insulin gene in the pancreatic beta cells that manufacture the sugar-regulating hormone.

Demonstrating enhancement

With the inventory of enhancers growing, investigators became ever more eager to learn how they worked. One conclusion seemed inescapable: cell-specific proteins play a significant role in triggering these sequences into action. The initial evidence for this conclusion came in 1982 when the Khoury and Schaffner teams independently detected measurable differences in host-cell response to different viral enhancers. They found the enhancer from monkey virus SV40 to be far more active in promoting transcription in monkey cells than in mouse cells. The reverse was true, however, when enhancers from viruses known to produce tumors in mice were introduced into the two cell types. Such a differential response presumably evolved from interactions with cellular molecules specific to each species (which could help explain why some animal viruses manage to infect only certain cells in an organism).

Cell-genome enhancers made the case for cell-specific proteins all the more compelling. When the discoverers of the immunoglobulin-gene enhancers linked only the enhancer-bearing sequences to test genes, and introduced this chimeric contruct into both B-lymphocyte and fibroblast cells, all three teams recorded the same results: Independent of their position or orientation, the enhancer sequences dramatically increased the expression of the linked test gene in the immune-system cells, but they had no effect on the test genes in fibroblasts, which are precursors of connective tissue. In similar trials, Rutter and his San Francisco colleagues linked enhancer-like sequences from the human insulin gene to another test gene (which codes for a procaryotic enzyme designated CAT), and then proceeded to transfer these recombinant constructs into either beta cells or fibroblasts. As expected, they found the level of gene transcription and CAT production in beta cells to exceed that in the fibroblasts.

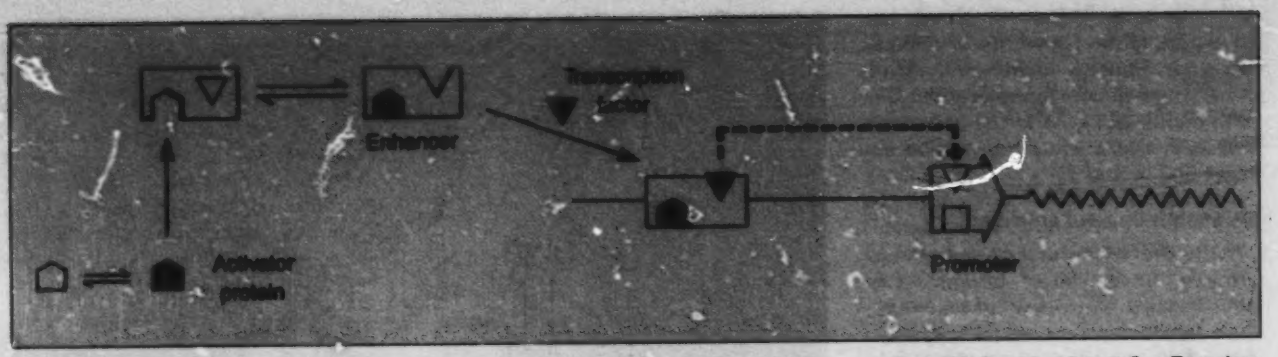
To date, about a dozen different cell-genome-derived enhancer sequences have been identified. The latest came in 1985, with the detection by Tom Maniatis and his colleagues at Harvard University of enhancing elements associated with the genes coding for human interferon, agents that fight off viral infection. However, not all have been tested to the same rigorous degree, says Robert Tjian of the University of California at Berkeley, and hence they may not all behave with the flexibility that characterizes enhancers. Tjian, who studies eucaryotic promoter function, notes that some enhancers have been found to have promoter-like sequences buried in them. Therefore, he explains, unless a putative enhancer is checked out from both the 5′ end and 3′ end of a gene, and from at least 1,000 base pairs away, there can be no certainty as to whether gene transcription is the result of enhancer or cryptic-promoter action.

Rutter. Linking sequences from a human insulin gene in pancreatic beta cells.

Enhancer triggers

At this point, says NCI's George Khoury, there is just no telling how many cellular enhancers there are—whether they are common or whether they are rarities restricted to just a few critical genes. "We could very well be overlooking any number of enhancers simply because we don't know exactly where to look or what to look for. Suppose, for instance, you see a sequence attached to a gene that doesn't fit the definition of an enhancer. That may be true only in that particular cell type. It could very well be an enhancer in another cell type, where it does fit the defi-

Tjian. Some enhancers have been found with promotor-like sequences buried in them.



Enhancer action. Protein and transcription factors bind to the enhancer that carries them in either direction along the chromosome until it reaches a promotor.

nition, because there specific proteins are being made by the cell that allow the sequence to function as a classical enhancer." As Khoury explains, much of the mistiness still surrounding enhancers may lift only after more is learned about the way enhancers actually work on a molecular level. That will not come, however, until proteins that activate these enhancers are identified and isolated; this has not yet happened, at least not for full-fledged cellular enhancers.

A comprehensive picture of the way such cell-specific proteins may work to bring enhancers to life and boost gene transcription could well emerge from viral studies being conducted at the University of California at San Francisco under the aegis of Keith Yamamoto. Since 1976 Yamamoto and his colleagues have been seeking to understand the way steroid hormones, which play key roles in many developmental and physiological functions, act to produce their various effects. For his research model, Yamamoto has long worked with a retrovirus that produces mammary cancer in mice. Designated MMTV, for mouse mammary tumor virus, it yields, upon invasion of mouse cells, a 9,000-base-pair DNA genome that takes up residence in the host's chromosomal DNA. Yamamoto discovered that this tumor-virus DNA, upon insertion into the cellular genome, was highly responsive to one class of steroid hormones, the glucocorticoids, which regulate protein and carbohydrate metabolism. It was more specifically responsive to dexamethasone, a synthetic analogue of the natural hormone, with which Keith Yamamoto prefers to work because of its easy stability.

Yamamoto proceeded to transfect cells from animals other than mouse with the viral DNA. As long as these host cells were themselves responsive to the hormone, as most animal cells seem to be, he continued to see a significant increase in viral gene transcription. When the hormone was removed, this activity subsided. In previous studies, he and others had shown that the hormone was linked to a glucocorticoid receptor protein in the cell. As a unit, protein and hormone traveled in tandem to the nucleus and acted selectively to increase viral-gene activity. Eventually, the Yamamoto team succeeded in pinpointing the sites where the hormone-altered protein bound to the MMTV DNA. This was in the so-called long terminal repeat, the region known to contain retroviral gene-control sequences.

By 1983 the scientists at San Francisco had enough evidence to conclude that the hormone's effects were being brokered through linkage with DNA binding sites that fit the now-classic description of an enhancer: an orientation- and position-independent sequence that sharply increases the capacity of the promoter to transcribe the genes under its control. It now appears that there are multiple specific enhancer sites distributed throughout the MMTV DNA, and a single eight-nucleotide sequence is common to all of the sequences that are susceptible to regulation by glucocorticoid receptors. Yamamoto suggests that this core sequence may be the site for which the receptor looks.

In late 1984 Yamamoto and his postdoctoral colleague Roger Miesfeld, in collaboration with reseachers from the the Karolinska Institute in Sweden, succeeded in cloning the gene that codes for the glucocorticoid receptor in the rat. This achievement has opened the way to production of the protein in

Zaret. Seeing what happens in the nucleus when receptor protein and enhancer bind.

Patrusky, the author of "Biology's Computational Future" in Mosaic *Volume 16 Number 3, was winner of this year's American Chemical Society Grady Stack award, an award in which 11* Mosaic *articles figured.*

Yamamoto. Success in finding sites where hormone-altered protein bound to DNA.

quantities far more substantial than were previously possible by way of its painstaking isolation from rat liver cells. Having an abundance of protein, as well as a variety of mutant versions of the protein, puts investigators in a better position to probe in detail the interaction of the receptor and the enhancer.

In vivo experiments

Ultimately, scientists would like to know why enhancers, activated by their specific protein triggers, go on to spur a step-up in gene transcription. One possibility is that the linkage induces a conformational change in the nuclear DNA. That change, in turn, sets the promoter up for a quicker availability of RNA polymerase, the enzyme that transcribes mRNA copies of the gene. Part of the evidence to support this idea of a change in DNA structure grows out of studies by biophysicist Kenneth S. Zaret, a postdoctoral member of the Keith Yamamoto team now at Brown University. Zaret set out to look at what happens in vivo—in the cell nucleus—when receptor protein and enhancer bind. "You don't have naked DNA in vivo," Zaret says. "In the chromosome, DNA is densely coated with histones and wound around still other proteins so as to be virtually inaccessible to enzymatic assault, unless avenues of approach are cleared."

In his studies, Zaret linked MMTV enhancer sequences to a strand of DNA containing a foreign gene, the herpes virus gene coding for the enzyme thymdine kinase, and its promoter. In initial trials, he showed that when these cells were exposed to dexamethasone, the introduced gene increased its enzyme production as much as 50-fold over what it would have been without the MMTV enhancer elements, and all within about 20 minutes of administration of the hormone analogue. What Zaret did next was cool the hormone-treated cells down to a few degrees above freezing, "enough to halt whatever's going on biochemically but not enough to kill." He then isolated and purified the nuclei from these cells with the chromatin (DNA plus histone proteins) intact and the glucocorticoid receptor attached (or unbound in the case of untreated cells serving as controls).

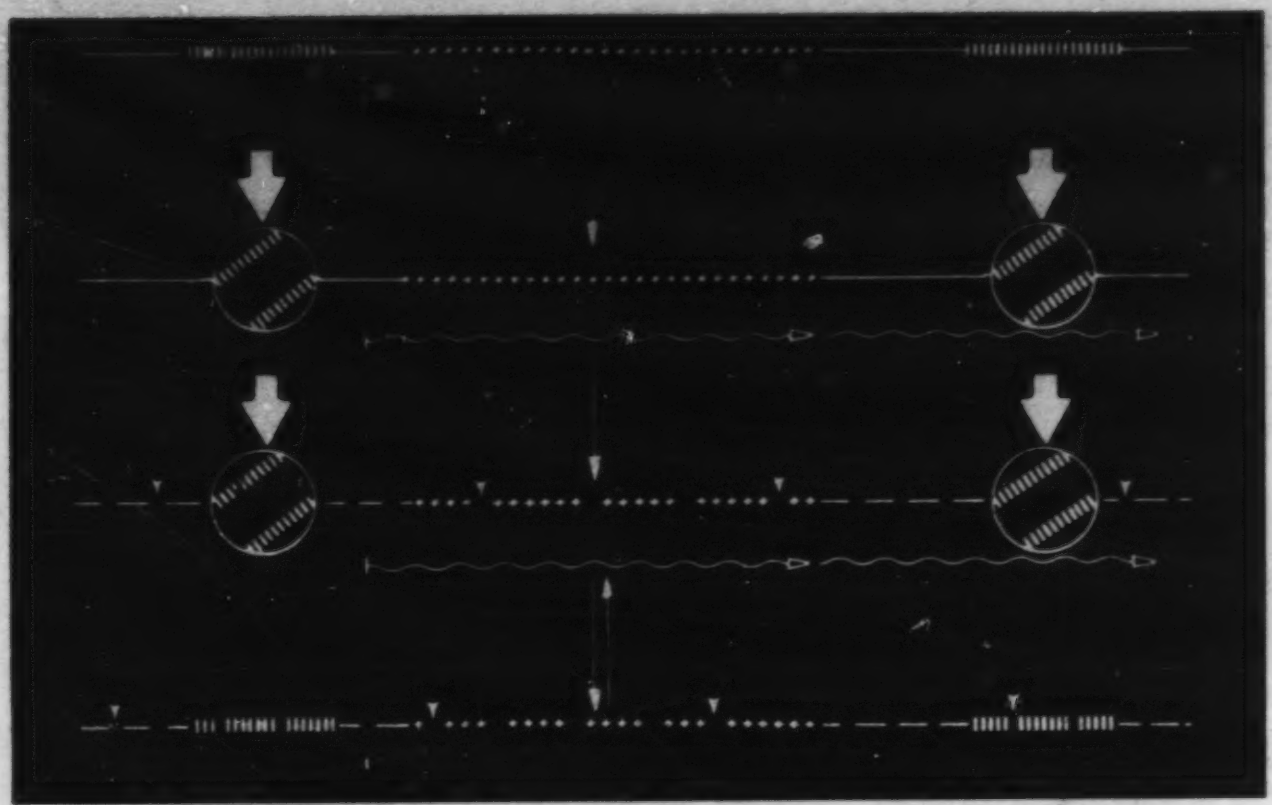
Zaret went on to expose these nuclear assemblages to a DNA-splitting enzyme, DNase I, in line with a technique first devised in the mid-1970s by Hal Weintraub and Mark Groudine of the Fred Hutchinson Cancer Research Center in Seattle. The strategy is based on the idea that the nuclease will cut most effectively where it can gain access to the DNA, presumably where the genome is no longer paved over with protein. When Zaret mapped these so-called hypersensitive sites, he found that they coincided with the region embraced by the bound receptor protein, the region inhabited by the MMTV enhancer sequences. Untreated cells, by contrast, showed no such DNase sensitivity.

Time dependence

Kenneth Zaret's findings seem to dovetail neatly with observations made by Gary Felsenfeld and his colleagues at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. Working with chicken beta-globin genes, which code for a protein critical to red blood cells, they discovered a region that was hypersensitive to nucleases, but only in cells from chickens that were at least nine days old—the time when the globin genes begin to be expressed. Red blood cells taken from younger chicks were found to have beta-globin genes that were resistant to DNA-chewing nucleases.

Subsequently, Felsenfeld and his colleagues identified at least two cellular factors—proteins yet to be completely isolated—that bind to the hypersensitive region, and that appear only when the globin genes are active. Felsenfeld is quick to point out that this region, located on a segment flanking the 5′ end, does not meet the definition of an enhancer and may actually be part of the promoter mechanism. His studies, however, suggest the way binding proteins act to create enhancer-hypersensitive regions. In simple terms, if the histones were beads on a DNA string, the proteins would work by spreading beads apart, baring the DNA below.

But the question is still begged: How do such conformational changes in enhancer elements generate an increase in gene transcription? Several models have been proposed. All are highly speculative but are not necessarily mutually exclusive. One possibility is that the hypersensitive sites give RNA polymerases access to DNA. Once on board the genome, these enzymes can crawl in either direction, given the nondirectionality of enhancer elements, to the nearest promoter, there to initiate the transcription process. Another possibility is that the activated enhancer transmits a signal, perhaps through modulation of DNA coiling, that opens the promoter to stimulation by its own specific set of triggering proteins. Still another possibility known as the bending model, the activated enhancer is envisioned as causing



Chromatin structure change. After hormone treatment, chromosome shows regions of hypersensitivity (large arrows) and moderate sensitivity (small arrows) to DNA-splitting enzymes. On subsequent withdrawal of hormone, moderate chromosomal sensitivity persists.

the DNA to twist in a manner that allows the enhancer's bound protein to interact directly with the promoter or its protein so as to allow stepped-up incursion by RNA-transcribing molecules.

Anti-enhancers

On the basis of procaryote models, it seemed likely that just as there were binding proteins to stimulate gene transcription, there might also be proteins to turn off or repress this function. In the case of eucaryotes, however, this would be not only by blocking promoters but also by hindering access to enhancers. Two such enhancer-dampening proteins, produced in the early stages of infection by a human adenovirus, came to light in 1984 in studies by Pierre Chambon and his Strasbourg associates. These proteins were found to repress activity of the SV40 and polyoma virus enhancers. Subsequently, they have been seen to have a similar effect on the cellular genes of antibody-producing immunoglobulin.

More surprising, however, was the discovery in 1985 of DNA sequences that fit the definition of enhancers, except that they acted in a completely opposite manner. Where enhancers serve to increase gene transcription, these sequences were seen to diminish promoter activity. They were first identified in yeast cells by Kim Nasmyth and his colleagues at the Medical Research Council Centre in Cambridge, England, and were given the name silencers. In 1986 George Khoury and his NCI colleagues reported finding a silencer linked to the higher-order rat-insulin gene. "We did all the manipulations," says Khoury. "We moved it from its natural 5′ position to the 3′ end. We flipped it. It still worked." There was one major difference: The silencer was less dramatic in its effect than was a corresponding enhancer; the silencer reduced transcription by a factor of about 10 while enhancers increase this activity 100-fold or more. Given the ostensibly mirrorlike relationship between silencers and enhancers, however, Khoury believes that in solving the mechanism of action of one, scientists will have gone a long way toward explaining the other.

Knowledge of enhancers grew from studies conducted in cell-free solution or in cell culture. However, there was no telling for sure if and to what degree these enhancer sequences come into play in the whole organism. This issue is now being addressed through the introduction of foreign genes into fertilized mouse eggs, leading to the birth of transgenic offspring; the added genes and accompanying control elements are part of the genome of each mouse cell. In one recent study, for example, Douglas Hanahan of Cold Spring Harbor Laboratory in New York State hooked a tumor-causing SV40 early gene to the control sequences of rat insulin and produced mice with this DNA combination in every cell. Expression of the gene, though, was detected only in the mouse beta cells, even to the point of tumor formation. This finding was a clear indication of tissue-specific enhancer activity. It was also confirmation of cell-culture studies conducted by William Rutter and his San Francisco colleagues. George Khoury's NCI team, meanwhile, in collaboration with scientists at the Johns Hopkins University School of Medicine, has succeeded in inducing neurologic disturbances in transgenic

mice dealt genes from a virus isolated from patients with a severe nervous system disease.

Tissue specificity

From such studies it is clear how research into enhancers and other regulatory elements is giving investigators a sharp new perspective on genetically based, tissue-specific diseases—cancer, diabetes, and muscular dystrophy among them. Concerning cancer, for example, there is now widespread conviction that many malignancies derive from native genes, natural members of the cellular genome gone awry. Called oncogenes, they bear strong homology to retroviruses known to produce mammalian tumors. Ordinarily, these genes lie dormant or under rigorous transcriptional control. With the loss of regulatory restraint, however, comes unmitigated cell growth and cancer.

One way this loss may occur is through insertion into the genome of control sequences, promoters and/or enhancers, brought in by invading viruses. In the wrong place, these elements could elicit inappropriate or enhanced expression of the oncogene, enough to trigger the malignant process. One well-documented example of this sort of phenomenon comes from studies of a retrovirus, the avian leukosis virus ALV, that stimulates tumor development in birds. As has been demonstrated, however—by Susan Astrin at Fox Chase Cancer Center in Philadelphia, William Hayward at the Sloan-Kettering Institute for Cancer Research in New York, and others in one collaboration, and by E. Varmus at the University of California at San Francisco in another—it is not the viral genes in themselves that cause the cancer. What happens instead is that integration of the viral DNA often places its promoter or enhancer elements at sites that enable them to provoke abnormal transcription of the avian cellular oncogene. Such enhanced understanding of the disease process could well lead to novel, more effective approaches to treatment.

Recognition of the role of enhancers in gene expression promises to be of benefit in still another clinical arena, namely gene therapy, now at the threshold of human trials. As Khoury explains, "Introduction of an enhancer-gene combination that is appropriately expressed in specific tissues might allow for the correction of a genetic dysfunction due to errors in endogenous genes." By the same token, a transplanted gene lacking the proper enhancer sequence may well remain silent and ineffective.

Felsenfeld. Discovering nuclease-hypersensitive region in beta-globin genes.

Evolution and differentiation

Discovery of enhancers also may prove a boon to the study of evolution. Scientists investigating the saga of life's emergence have generally been impressed by the ostensible rapidity with which evolution seemed to have happened, at a rate that was far too quick to be attributable solely to simple mutations (for example, base-pair changes and sequence deletions). "But," asks San Francisco's Keith Yamamoto, "what if enhancers themselves were transposable elements, movable pieces of DNA, that could pounce around the genome? Even if this happened at a very low rate throughout evolution, we could see some likely outcomes." Yamamoto cites the glucocorticoid enhancer GRE as an example. "Imagine having a promoter sitting on a genome and a GRE comes along. That promoter would now suddenly be under hormonal control. What's particularly significant is that with enhancers you don't have to have the element land in a perfect place. It doesn't matter which way it's facing when it lands, whether upstream or downstream. It just has to be close enough to the promoter."

Botchan. First to discover a naturally occurring downstream enhancer in a virus.

As many scientists see it, the story of evolution devolves more from change in the rate at which certain genes are transcribed than from change in the structure, the coding sequences, of those genes. Says Yamamoto, "With enhancers, evolution becomes very efficient. You don't have to change a base pair at a time hoping that maybe in ten million or more years that mutation will make it possible to bind a receptor that increases transcription, only to find out that the change was not so evolutionarily hot after all. On the other hand, what if, instead, an already available, already invented control element moved into place? That would sure shortcut things. Nature likes efficiency. So I can certainly see how evolution would lock onto such a scheme."

For many molecular biologists the ultimate excitement about enhancers stems from the growing conviction that these control elements will bring them much closer to resolving the mystery of differentiation. In that quest, says Michael Botchan of the University of California at Berkeley, there is little doubt that viruses will continue to serve as the primary research vehicle. Says Botchan, who was first to discover a naturally occurring 3' (downstream) enhancer, in the wart-causing papilloma virus, "At its root, differentiation means switching genes on and off at the right time. In truth we don't yet know how viruses do that, let alone organisms. And so, many of us are working on trying to figure out how a virus, with its arsenal of promoters and enhancers, manages to change its program of transcription—from when it first enters a cell and makes one set of proteins to a point later on when it starts making something else. We are not out to solve differentiation per se. But we believe that by focusing on something really small and solving it, we will eventually come to understand everything."

Put another way: "Think small, talk big." Investment in this research model has certainly given investigators a giant harvest of dividends. As Botchan intimates, there is clearly no reason to believe that faith in the axiom will prove less rewarding in the future. ●

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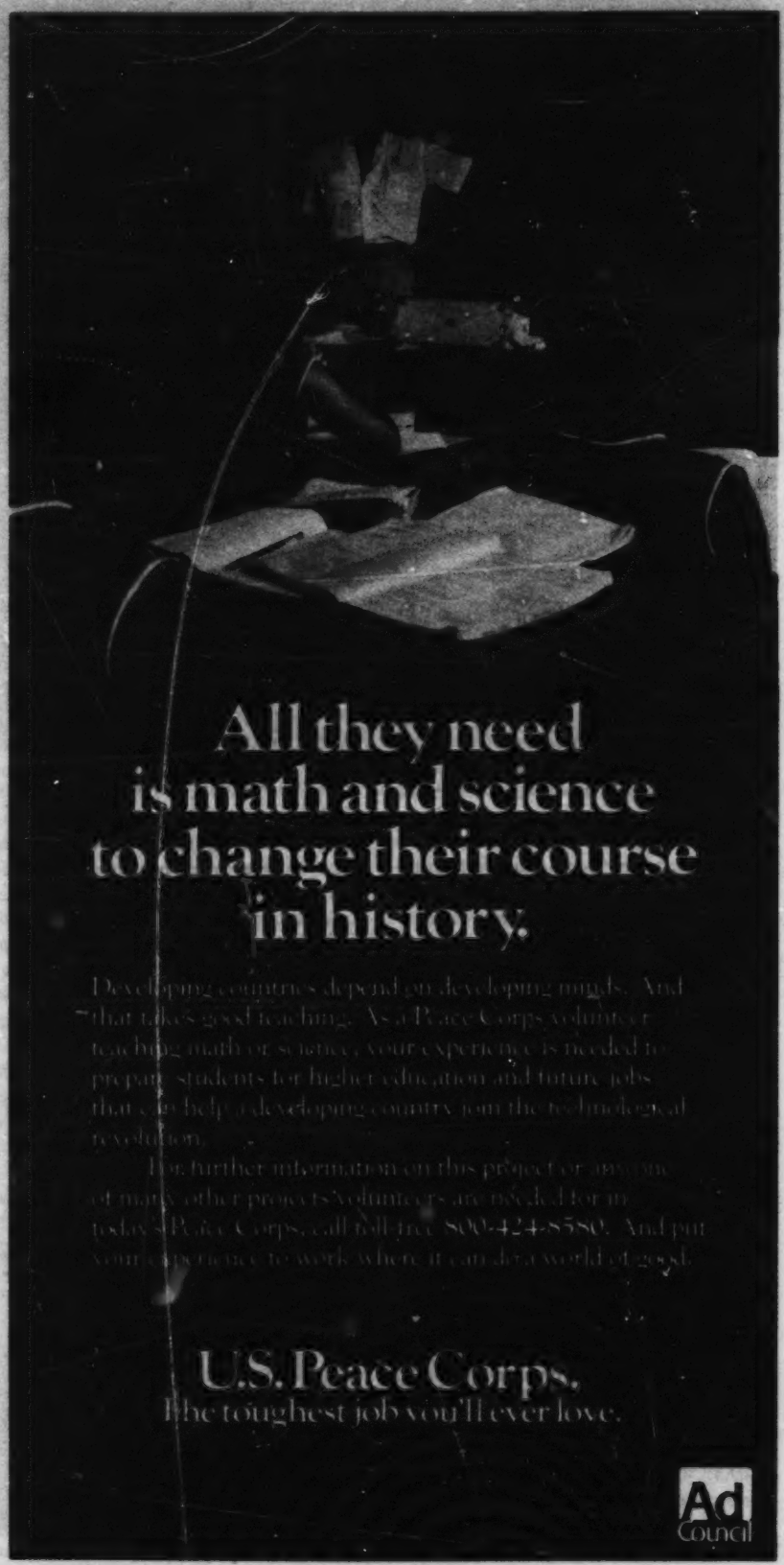

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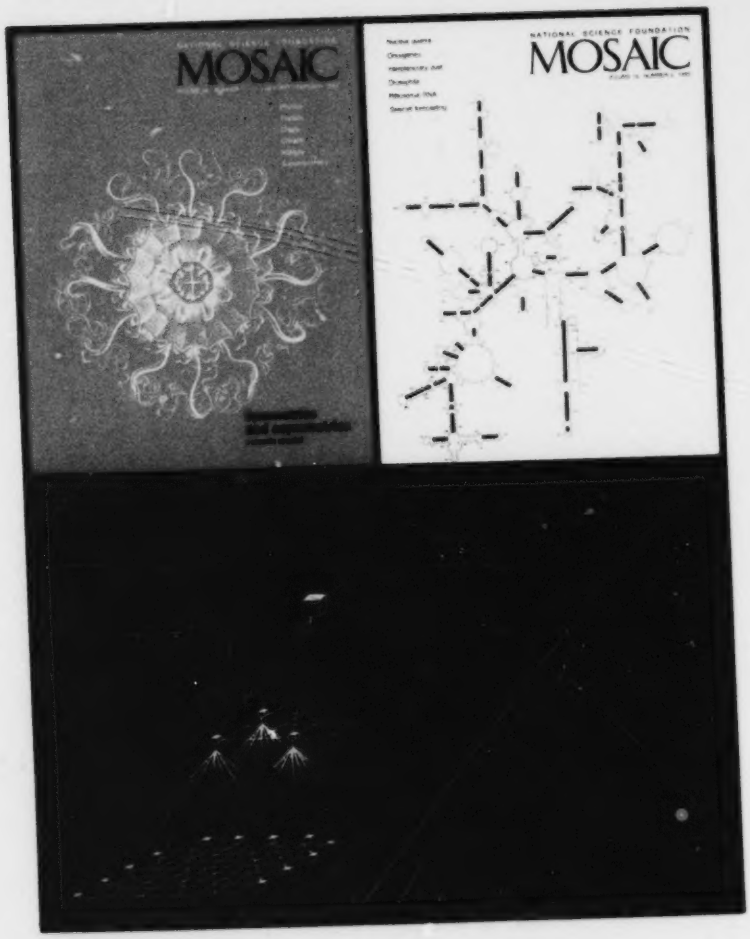

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Science & Engineering Doctorates to U.S. Citizens Decline

The number of U.S. citizens who received science and engineering (S/E) doctorates in 1985 declined 3 percent from the previous year to 12,600, the lowest level since 1968.[1] This decline reflects a general trend that has persisted for nearly 15 years.

S/E doctorates awarded by U.S. universities to U.S. and foreign citizens peaked at 19,000 in 1972 and 1973. The number declined through 1977 to 17,080 and then increased gradually by 7 percent to 18,255 in 1983. During the 1973-78 period there were decreases in the number of doctorates awarded to both U.S. citizens and noncitizens, but the proportion of doctorates earned by U.S. citizens remained relatively stable at approximately 80 percent. Since 1978, however, the number of S/E degrees earned by foreign citizens has increased while that of degrees earned by U.S. citizens has continued to decline. By 1985 the U.S. share of S/E degree holders had dropped to 72 percent.

The decline in S/E doctorates to U.S. citizens overall reflects the net effect of four distinct trends, with differences between engineering and sciences and between men and women.

Awards in engineering increased in 1985 for both U.S. males and females. The increase for women continued a strong 7-year trend, when awards nearly quadrupled though remaining under 10 percent of the U.S.-citizen total. For males, a second successive year of increase was recorded after more than a decade of general decline. During the 1970-83 period, the number of U.S. males earning engineering doctorates fell by more than half.

The general decline in science awards to U.S. citizens, while evident in all fields, has been most severe in mathematics, where doctorates dropped by nearly 60 percent between 1970 and 1985. The trends in science awards for men and women differed from the patterns for engineering. The number of U.S. males receiving science doctorates in 1985 continued a virtually uninterrupted 14-year decline. The 30 percent fewer awards to males in 1985 than in 1970 amounts to a difference of more than 3,400 degrees, which is a number greater than the combined total of this nation's men and women in engineering.

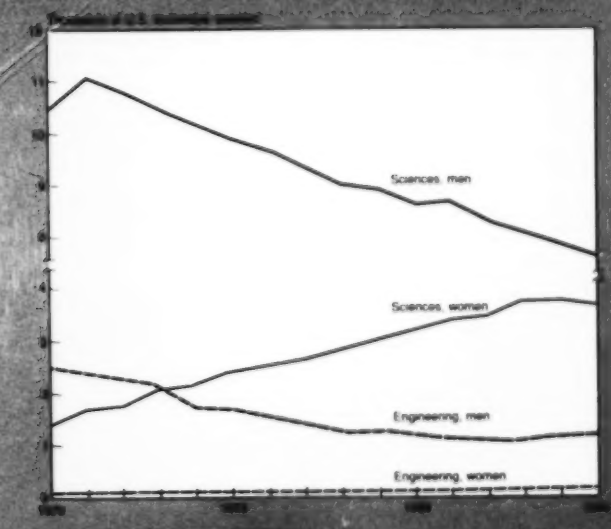
In contrast to the trend for men, the number of science doctorates to U.S. women continued to increase through 1984, though more slowly in the eighties. The slight decrease of 2 percent in 1985 resulted from declines in the three science areas where the participation of women has been proportionally highest: biological sciences, social sciences, and psychology.

The patterns for women's representation in S/E fields is repeated in non-S/E fields, where women traditionally have had higher representation. For example, in education the proportion of degrees earned by U.S. women rose from 20 percent in 1970 to 46 percent in 1980 and 54 percent in 1985. And in English and American language and literature, the increases were from 30 percent in 1970 to 49 percent in 1980 and 56 percent in 1985.

Most of the trends in doctorate awards observed here are likely to continue, based on a review of fulltime graduate enrollment in S/E fields. The substantial S/E enrollment increases among full-time women graduate students that marked the early eighties have ceased or reversed in some science fields, such as social sciences and environmental sciences. Similarly, among foreign students the rapid enrollment increases in doctorategranting institutions in the early eighties have slowed or reversed in all broad fields. Thus, there may be only slight to moderate increases in degree awards to U.S. women and to foreign citizens in the near future.

[1] The Survey of Earned Doctorates is conducted annually by the National Research Council for the National Science Foundation, the National Endowment for the Humanities, the National Institutes of Health, and the Department of Education. Approximately 95 percent of the 1985 recipients of the Ph.D. and similar doctorates (such as Ed.D.) responded to the survey questionnaire. The database also includes some information on nonrespondents that was obtained from public sources. Recipients of first-professional degrees (the M.D. degree, for example) are not included.

Science and engineering doctorates earned by U.S. citizens



S/E doctorates to U.S. citizens: 1970 and 1985